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*"I would have everie man write what he knowes and no more."*—MONTAIGNE

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# Partial liquid ventilation—turning back a PAGE on evolution

On an evolutionary time scale, liquid ventilation is not new. Land-dwelling vertebrates derived from fish 350 million years ago, and fish continue to breathe through a liquid medium. However, the ability to sustain mammalian respiration artificially by a liquid ventilation technique is generally accredited to work in the early 1960s, where mice were kept alive breathing hyperbaric salt solutions.[1] The hyperbaric conditions were required in order that sufficient oxygen could be dissolved in solution to sustain cell respiration.

This was taken further by Clark and Gollan in 1966 when they described the use of silicone oils and fluorocarbons at atmospheric pressure in supporting the life of mice and cats receiving a liquid ventilation technique.[2] Silicone oils were found to be too toxic to use in living creatures but the perfluorocarbons showed more promising characteristics. Perfluorocarbons (PFC) are a group of stable, inert, colourless and odourless liquids which are not soluble in either lipids or water. Oxygen, carbon dioxide and most other gases, however, are dissolved. The solubility of oxygen in PFC is of the order of 50 ml per 100 ml of solvent, and carbon dioxide 200 ml per 100 ml of solvent at atmospheric pressure (i.e. 20 and three times the solubility of each gas in plasma, respectively). They have a low predisposition to react with biological tissue. PFC may be derived from organic compounds (e.g. benzene) by replacement of carbon bound hydrogen atoms with fluorine, by heating the organic compound with cobalt trifluoride or by electrochemical fluorination techniques.[3]

Throughout the 1970s and 1980s, further work was done in animals, both with normal lungs[4] and in models of prematurity and lung injury.[5 6] Two milestones have been reached in the past 10 yr. First, until recently liquid ventilation required relatively complex extracorporeal equipment to oxygenate and remove carbon dioxide from the liquid medium. This involved filling the functional residual capacity with PFC and using tidal volumes consisting entirely of liquid, and was known as (total) liquid ventilation. Fuhrman, Paczan and DeFrancisis[7] described how it was possible to sustain ventilation in pigs with a hybrid technique, that is a medium of perfluorocarbon but using a standard ventilator (so called perfluorocarbon associated gas exchange (PAGE) and also known as partial liquid ventilation (PLV)), while Greenspan and colleagues described the first human use of this respiratory medium (in preterm infants with respiratory distress syndrome).[8 9]

Within the past year there has been the publication of the first human experience of this technique in acute respiratory distress syndrome in adults.[10 11] The 10 adult patients cited were already being supported by extracorporeal gas exchange. These studies were uncontrolled, but appeared to show that instillation of the PFC Perflubron ($C_8F_{17}Br$) was "safe in these patients with severe respiratory failure receiving extracorporeal life support and may be associated with improvement of gas exchange and pulmonary compliance".

In addition to their characteristics quoted above, the mode of action of PFC is speculative at present. PFC are dense although not appreciably more viscous than water. They therefore accumulate in the most dependent parts of the lung. This density implies that inflammatory debris "floats" on top of the PFC and, as it were, is lavaged out of the alveoli. Furthermore, PFC have a low surface tension (for example Perflubron has a surface tension 18 dyn $cm^{-1}$).[11]

It has been speculated that Perflubron opened up previously collapsed segments in the most dependent parts of the lung making them available for gas exchange, that is expanding functional residual capacity. The surface tension reducing properties may help to keep the re-opened alveoli expanded, essentially a surfactant-like function. It was also argued that the density of the PFC displaced some blood to the non-dependent (better ventilated) portions of lung, optimizing ventilation/perfusion matching.[11]

Further, the lavage of inflammatory mediators could have played a role by acting as continuing "fuel" for substances causing capillary leak in addition to washing out proteins which inhibit surfactant function.

What is unclear is how much gas exchange actually occurs through PFC themselves, as opposed to gas exchange through aerated lung tissue.[12] Hirschl and colleagues did not mention if they pre-oxygenated the PFC before administration. Animal work using PFC equilibrated with 100% oxygen noted only slight deterioration in oxygenation immediately after administration, and the conclusion drawn from this was that the PFC itself contained a "reservoir" of oxygen which continued to supply oxygen during the transition period from gas to liquid ventilation.[7] One could postulate however, that there might be a more marked transient decrease in oxygenation if non-equilibrated PFC were used.

The only problems resulting from Perflubron, according to Hirschl and colleagues, seemed to be mucus plugging, which was relieved by more vigorous suction. Pneumothorax occurred in five patients during PLV, but only in one who did not already have a chest drain for pre-existing pneumothoraces.

More general concerns with regard to the use of PFC include slow elimination from the body. A study in beagles showed traces of the PFC Caroxin-F in the lung (but also liver, kidney, spleen, heart, brain skeletal muscle and fat) 3 yr after 1-h exposure to liquid ventilation. Elimination of this PFC is primarily by evaporation and removal via the lymphatics. Not surprisingly therefore, the highest concentrations were noted in the lungs and associated lymph nodes. There was also an increase in serum alkaline phosphatase and cholesterol concentrations with an elevated peripheral white cell count, which returned to normal within a week. Follow-up platelet counts at 6 and 9 months were reduced significantly, although still within the normal range.[13]

Despite these findings, there were no histological structural changes in the lung, liver, spleen, kidney, heart or brain attributable to PFC. There is, however, understandable anxiety in using an agent which is retained in the body for so long, even if it apparently does no harm.

On an important practical note, the radiodensity of the PFC makes interpretation of chest radiographs difficult for several weeks after administration. It is also believed that deep sedation may be required.[12] There is also the possibility (which is true of mechanical ventilation in general) that there may be impairment to venous return,[12] although Hirschl and colleagues found no change in cardiac index.

Current knowledge suggests a clinical potential. It may be a means of providing some of the benefits of surfactant therapy (as yet still experimental in acute lung injury, compared with its established place in the treatment of immature, surfactant deficient lungs), in addition to applying a graded degree of PEEP where it is needed most in ARDS (in collapsed, dependent lung areas). By reducing inappropriate overdistention of the lung, this could limit iatrogenic lung damage.

Whether these theoretical benefits can be translated into reality depends on further research. Without further investigation into this form of therapy, we may be missing the opportunity of a useful novel adjuvant therapy to support the injured lung, to add to other novel treatments such as inhalation of nitric oxide and extracorporeal lung support.

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*British Journal of Anaesthesia* 1997; 78: 3–9

CLINICAL INVESTIGATIONS

# Absence of memory for intraoperative information during surgery under adequate general anaesthesia

I. F. Russell and M. Wang

## Summary

Using the isolated forearm technique (IFT), we wished to determine if patients known to be unresponsive to commands during general anaesthesia with nitrous oxide, halothane and neuromuscular blocking agents had any evidence of explicit or implicit recall. Two groups of women, studied in a single-blind sequential block design, heard different tapes, either a command and information tape ($n$=34) or radio static ($n$=34), throughout surgery. Four women (two radio static, two command) had unequivocal evidence of explicit recall for a period near the beginning or end of the procedure, at a time when the IFT was not being used. With or without hypnosis, category generation, serial position of category exemplars and word association tests did not reveal evidence of priming. We conclude that during light general anaesthesia with nitrous oxide, halothane and atracurium, patients had neither explicit nor implicit memory for information presented during a period when they are known to be unresponsive to commands. (*Br. J. Anaesth.* 1997; **78**: 3–9)

**Key words**
Anaesthesia, depth. Anaesthesia, general. Memory.

Over the past few years a belief has developed that postoperative tests of implicit memory (i.e. no explicit recall of a learning episode but test performance is altered) reveal that patients can process and recall auditory information presented to them during general anaesthesia. This subject has been discussed in depth at three international symposia entitled "Memory and Awareness under Anaesthesia".[1–3] Although results are mixed, virtually all of the evidence suggesting patients can process information during general anaesthesia has been obtained in patients undergoing surgery where neuromuscular blocking agents were used as an integral part of the anaesthetic technique.[4 5]

The use of the isolated forearm technique (IFT) has revealed that with some general anaesthetic techniques more than 70% of patients may be capable of responding to commands during surgery with no postoperative conscious (explicit) memory for these intraoperative events.[6–8] Clinical monitoring of arterial pressure, heart rate, sweating and tear production was of little benefit in predicting the conscious state of patients during surgery and no clinically useful relationship could be found between changes in these clinical variables and a patient's responses.[9] Further evidence that clinical signs cannot be used to determine reliably the occurrence of intraoperative awareness comes from another study where anaesthetic records were examined in detail after surgery: three experienced anaesthetists were unable to identify the anaesthetic records of patients known to have been aware during surgery from the records of matched controls who had not been aware.[10]

A major flaw in the methodology of studies investigating implicit memory in relation to general anaesthesia lies in the assessment of "adequate" anaesthesia. These studies used no direct means of establishing the conscious level of patients during anaesthesia, relying instead on clinical monitoring, an indirect, unreliable and imprecise method of assessing conscious levels in the presence of neuromuscular blocking agents.[11] Thus it is possible that in these previous studies clinical monitoring suggested adequate anaesthesia but all patients may not have been unconscious. If patients are awake during surgery, even with no explicit recall, then it is perhaps not surprising that sophisticated psychological tests reveal evidence of implicit memory.

While using the IFT we wished to investigate the occurrence of postoperative implicit recall when information was presented to patients during surgery at a time when they were non-responsive to commands.

## Patients and methods

Approval for the study was obtained form the Hull and East Yorkshire Ethics and Clinical Trials Committee. Informed consent was obtained from women (ASA I or II) with no hearing difficulty presenting for major gynaecological surgery. The possible use of hypnosis on day 3 was mentioned, but patients were advised that the use of hypnosis was

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optional and that separate consent would be obtained at that time.

After premedication with temazepam 20 mg orally, 1–2 h before operation, and after baseline readings had been obtained from the monitoring system, anaesthesia was induced with thiopentone 5 mg $kg^{-1}$. As soon as consciousness was lost (absence of response to command) 66% nitrous oxide in oxygen with halothane (0.5% set on the vaporizer) was commenced by manual mask ventilation. After tracheal intubation, facilitated by suxamethonium 1.5 mg $kg^{-1}$, mechanical ventilation of the lungs was continued with this same gas mixture via an Oxford Penlon mark II ventilator in its non-rebreathing configuration. End-tidal carbon dioxide concentration was maintained at 4–5%. When the action of suxamethonium began to wear off, atracurium 0.2–0.4 mg $kg^{-1}$ was used for more prolonged neuromuscular block.

The study included extensive automatic monitoring (with recording to computer hard disk) of haemodynamic, EEG and other psychophysiological variables, details of which are available from the authors. These data are not reported here as intraoperative cognitive status was determined directly using the IFT, as described in table 1. "Rescue" anaesthesia was built into the study design such that if the isolated forearm revealed persistent reflex movements or semi-purposive movements or a response to commands, the patient would receive thiopentone 1.5 mg $kg^{-1}$.

The IFT commands were incorporated into a prerecorded stimulus tape and the patients formed two groups, studied in a single-blind, sequential block design. Within 2 min of skin incision one of two continuous loop cassette tapes was played to the patient through open headphones. One group heard radio static throughout surgery (group RSG), while in the other group (group CG) a 1-min continuous loop cassette tape containing two commands was played. This latter tape contained two discrete 15-s messages (separated by 15 s). Each message was preceded by the patient's preferred name (twice) and the words "this is Dr Russell speaking": the first message was "if you can hear me I would like you to open and close the fingers of your right hand, open and close the fingers of your right hand"; the second message was "here are some special words I would like you to remember—"sour gooseberry, sharp lemon, green pear".

*Table 1* Summary of the isolated forearm technique

1. A padded arterial pressure cuff is placed around the right forearm
2. ECG electrodes, connected to a Relaxograph, are placed over the ulnar nerve just above the elbow joint and over the median nerve in the cubital fossa. Recording electrodes placed over the wrist and hypothenar eminence.
3. Anaesthesia is induced and a supramaximal stimulus obtained.
4. An appropriate dose of suxamethonium is administered for tracheal intubation and the patient is connected to the ventilator.
5. The response from the Relaxograph is checked.
6. As suxamethonium wears off the tourniquet is inflated and an appropriate dose of atracurium is administered.
7. Start the tape recorder.
8. Assess neuromuscular integrity at regular intervals.
9. Deflate the tourniquet at 20 min.
10. If further neuromuscular block is required re-inflate the tourniquet and administer a small dose of atracurium.
11. Repeat steps 8, 9, 10 as necessary

*Table 2* An example of the simple questions asked early in the interview, and the later cue questions used to elicit evidence of explicit memory

Simple questions
1. What was the last thing you remember before going to sleep?
2. What was the next thing you remember?
3. Can you remember anything in between?

Cue questions
I said I would play a tape recorder to you during surgery:
1 Do you know what was played to you on the tape?
2. Do you remember hearing anything?
3. Do you remember hearing anyone talking to you?
4. Do you remember anyone asking you to do anything?
5. Do you remember anyone asking you to do anything with a hand or arm?
6. Do you remember anyone asking you to do anything with your right hand or arm?

The tape was switched off before halothane was discontinued during skin closure. Residual neuromuscular block was antagonized , if required, with 0.5–1 ml of a glycopyrronium and neostigmine mixture (ratio 0.5 mg/2.5 mg in 1 ml). After extubation, papaveretum 0.5 ml i.m. and 0.5 ml i.v. was administered and the patient taken to the recovery room.

One to two hours later patients had a structured interview to elicit any conscious memories of the surgical period, of the tape played to them or evidence of dreaming. Cue questions which did not presuppose a particular answer were used to elicit evidence of factual recall (table 2). Patients were then asked to name five vegetables and after their answers were asked to name five fruits. A word association test was then performed with the following words, "father", "hill", "sour", "sharp", "green". Thus the study included three different types of probe for the same intraoperatively primed words: free (explicit) recall, word category and word association (implicit recall).

On the third day, patients were seen again and asked if they would consent to a second interview under hypnosis. If consent was not obtained for hypnosis then the original interview was repeated. If consent for hypnosis was obtained, patients walked to a side room and sat in a padded armchair with their forearms and hands resting on the arm rests. After a standard hypnotic induction the trance was deepened using a visualization technique and arm levitation. When hypnosis was thought to be adequate (i.e. arm levitation occurred) the patient was regressed to the preoperative period to the time when she was lying in bed awaiting transfer to the operating theatre. She was then asked to describe her feelings and the various events she experienced from that time to the present.

Because of the vivid "real life" experiences possible under hypnosis (Bennett, personal communication) it was felt essential to ensure that contact was maintained with the patient at all times to reduce the chance of some untoward occurrence. Thus just before the patient's experience of anaesthesia was investigated under hypnosis the following reassurance was given: "very soon you will be going off to sleep with your anaesthetic and I would like you to tell me what it feels like as you go off to sleep and what you are aware of as you go off to sleep. This time you will be able to speak to me and to hear me and you will be able to breathe normally; things you may not have been able to do during your anaesthetic". The original recovery interview was then repeated under hypnosis. Before wakening from hypnosis the women were advised that they would remember only as much of the hypnotic interview as they wished. General reassurance about recovery from surgery, mobility and ego strengthening were the final aspects of the hypnotic session.

If arm levitation was not obtained the interview continued (as described above), but the results were analysed as belonging to the appropriate non-hypnosis group.

Results were analysed using *t* tests,· chi-square tests and signal detection tests,[12] as appropriate.

## Results

We included 68 woman who were studied sequentially in the following single-blind manner: 17 command tape, 17 radio static, 17 radio static, 17 command tape. Some patients could not be interviewed adequately in recovery and others were not seen on day 3, hence the variation in numbers within the subgroups. Of those seen on the third day, seven women in group CG and 13 in group RSG refused hypnosis. This difference was not significant (chi-square test $P$=0.096).

*Table 3* Type of surgery, patient age, weight, time from induction to skin incision and duration of exposure to tape (mean (SD or range)). AH = Abdominal hysterectomy, VH = vaginal hysterectomy, other = other major gynaecological surgery. *Chi-squared test; †*t* test.

| | Group RSG | Group CG | *P* |
|---|---|---|---|
| Type of surgery | | | |
| AH (*n*) | 23 | 21 | ns* |
| VH (*n*) | 5 | 11 | ns* |
| Other (*n*) | 6 | 2 | ns* |
| Age (yr) | 43.7 (17–57) | 42.9 (30–67) | ns† |
| Weight | 65 (12.2) | 64.7 (10.1) | ns† |
| Time to skin incision (min) | 10.6 (2.6) | 9.5 (3.1) | ns† |
| Tape Exposure (min) | 44.3 (14.05) | 44.4 (14.25) | ns† |

*Table 4* Number of patients with possible recall or dreams on day 3. [a]Aware of voices and a buzzing noise suddenly blocking them out. [b]Aware of someone opening her eyelid, using her name, voices and a buzzing noise blocking things out [c]Aware of talking; someone cutting her lower abdomen. [d]Aware of people "doing things down there". [e]Aware of talking; also wanted to move fingers but could not. [f]Claimed to hear voice during anaesthesia: no reference to the radio static. [g]claimed to hear voice during anaesthesia: no reference to the radio static [h]Claimed to be aware of surgery, but described a laparoscopy PO = After operation (See appendix for a more detailed description of events pertaining to the above patients)

| | Group RSG (*n*=28) | | Group CG (*n*=31) | |
|---|---|---|---|---|
| | Hypnosis (*n*=15) | No hypnosis (*n*=13) | Hypnosis (*n*=24) | No hypnosis (*n*=7) |
| Evidence of recall | 1[a] | 1[b] | 3[c,d,e] | 0 |
| Other memory | 3[f,g,h] | 0 | 0 | 0 |
| Bad dreams | 3 (2-PO) | 0 | 1 (PO) | 0 |
| Good dreams | 0 | 0 | 2 | 0 |

The time from induction of anaesthesia until skin incision, duration of tape exposure and other patient data are presented in table 3. There were no differences between the groups.

No patient responded to commands during surgery but two patients in group RSG and eight in group CG exhibited reflex responses to surgical stimulation (Fisher's exact test $P$=0.032). Both patients in group RSG exhibited reflex responses at skin incision and one had reflex movements later during uterine traction. Seven patients in group CG exhibited reflex movements at skin incision and two had reflex movements during uterine traction. The remaining patient in group CG responded reflexly during uterine traction.

Initially, with superficial questioning, no evidence of explicit recall for intraoperative events was obtained during any of the interviews. However, with specific prompting cue questions (table 2), five women provided evidence of explicit recall (table 4).

Tables 5–7 summarize the data with respect to investigation of implicit memory. Analysis of simple word counts (chi-square test), analysis of scores based on the serial position of target words in the list (*t* test) and application of signal detection tests[12] did not provide evidence of priming for target fruits in group CG. In a previous investigation of women presenting for gynaecological surgery in the same hospital, Charlton[5] established the normative frequency of occurrence of common fruits in response to a request "name the first five fruits that come to

*Table 5* Number of patients who included the "target" fruit in their list of five fruits in recovery Patients responding with both "pear" and "lemon" are also included in individual counts of "pear" and "lemon"

| | Group RSG (*n*=30) | Group CG (*n*=31) |
|---|---|---|
| Pear | 16 | 14 |
| Lemon | 4 | 3 |
| Pear and lemon | 3 | 1 |
| Gooseberry | 0 | 0 |

*Table 6* Number of patients who included the "target" fruit in their list of five fruits on day 3. Patients responding with both "pear" and "lemon" are also included in individual counts of "pear" and "lemon". There were no significant differences in word category frequencies between the groups CG and RSG whether or not they are subdivided according to hypnosis There was no significant difference between the numbers consenting to, or achieving, hypnosis between groups RSG and CG

| | Group RSG (*n*=28) | | Group CG (*n*=31) | |
|---|---|---|---|---|
| | Hypnosis (*n*=15) | No hypnosis (*n*= 13) | Hypnosis (*n*=24) | No hypnosis (*n*=7) |
| Pear | 9 | 10 | 13 | 6 |
| Lemon | 2 | 1 | 5 | 1 |
| Pear and lemon | 2 | 0 | 2 | 1 |
| Gooseberry | 0 | 0 | 0 | 0 |

*Table 7* Control norms for the category "fruits" in the hospital population under study and the responses of groups CG and RSG in recovery and on day 3. Values represent the percentage of women responding with the given fruit in their list of five fruits. *These control norms were obtained for gynaecology patients in Hull from a previous study.[5] There were no significant differences between the control norms and groups CG or RSG groups. Rec = Recovery

| Fruit | Control* | Group CG (rec) | Group RSG (rec) | Group CG (day 3) | Group RSG (day 3) |
|---|---|---|---|---|---|
| Apple | 95 | 96 | 97 | 100 | 96 |
| Orange | 84 | 86 | 97 | 90 | 96 |
| Banana | 76 | 64 | 67 | 77 | 75 |
| Pear | 55 | 50 | 53 | 61 | 68 |
| Lemon | 12 | 11 | 13 | 19 | 11 |

mind". The responses of groups RSG and CG, both in recovery and on day 3, were not different from each other or from this previously obtained norm (table 7).

No patient at any time, with or without hypnosis, replied with an appropriate response in the word pair test.

Overall these tests for implicit memory of intraoperative information indicated no differences between groups RSG and CG and thus no evidence of a priming effect as a result of the command tape. There was no evidence that hypnosis, as performed in this study, enhanced recall of the primed words.

## Discussion

It is generally accepted that explicit recall for intraoperative events or information is evidence of inadequate anaesthesia. Thus, by this criterion, five women were inadequately anaesthetized at some stage of the procedure. None of the five patients was aware of pain and only one was aware of surgery. All episodes of recall occurred during a period when the IFT was not in use (see appendix for individual patient details).

As the tape recorder was not switched on until shortly after skin incision, there is little doubt that the two women in group RSG (table 4, superscripts "a" and "b") who described voices suddenly being blocked out by a buzzing noise were awake during the early part of surgery. Neither of these women was aware of surgery and it is not known for how long they remained awake after skin incision. Interestingly, after the day 3 interview, patient "a" volunteered that she had been awake during a previous Caesarean section: this had not been mentioned during the preoperative discussions.

Three patients in group CG (table 4, superscripts "c", "d", "e") also produced evidence of being awake momentarily during surgery. Patient "c" recalled hearing voices, but not what was being said, and was aware of skin incision: this was not painful and she drifted off to sleep. On discontinuing halothane, patient "d" awoke more quickly than expected, just as the surgeon was inserting a vaginal pack at the end of vaginal hysterectomy: she recalls someone "doing something down there". Patient "e" exhibited six reflex responses over a 15-min period with no other clinical signs of light anaesthesia, but unfortunately a few minutes after receiving her single incremental dose of atracurium the IFT cuff burst and deflated, with paralysis of the arm until the end of surgery. On the third day as she emerged from her hypnotic state she was observed to be opening and closing the fingers of her right hand. When asked why she was doing this she said she had wanted to "straighten and relax her fingers like this" while under hypnosis but had been unable to do so.

There seems little doubt that "c" was awake during the early part of the procedure and "d" at the very end, but before accepting the experience of patient "e" at face value, the responses of the three women in group RSG should be noted (table 4, f, g, h) who, under hypnosis, claimed to have had recall. The first of these was sure that the first author (I. F. R.) had asked her to do something with her hand; the second believed the first author (I. F. R.) spoke to her reassuringly during surgery. If these are real memories then they occurred either very early or very late in the procedure, before or after the radio static tape, at a time when anaesthesia may have been incomplete. The third patient in group RSG claimed to have been aware of surgery and when asked to describe her experience she clearly described a laparoscopy: whether this was related to her own previous diagnostic laparoscopy or to a recent television programme on laparoscopic surgery which she had watched is unknown. Nevertheless, despite the possibility of fabrication, the experience described by patient "e" as she emerged from hypnosis corresponds so precisely to actual intraoperative events that it seems extremely likely that she did indeed have recall for a period when anaesthesia was less than adequate.

It is of interest that none of the five women with evidence of recall voiced this during the interview in recovery. On the contrary, of the four patients capable of answering the questions, recall was specifically denied in recovery. This finding adds further to the confusion surrounding the issue of the most appropriate time to interview patients in the postoperative period. If subjects are interviewed in the immediate postoperative period then the residual effects of general anaesthetic drugs undoubtedly has some effect on cortical function. On the other hand, delaying a test too long may lead to degradation of the specific memory trace and thus reduce the likelihood of linking intraoperative information with postoperative recall. On balance, Bennett[13] believes that the evidence does not favour testing memory "as soon after surgery as possible". To add further to the difficulties, the optimum time for testing recall may vary depending on which memory function is being tested, "from a few minutes to a few days".[4]

Despite previous results to the contrary[14 15] there was no evidence that hypnosis, as used in this study, improved recall of primed words. Possible reasons for lack of enhanced hypnotic recall in this study could be: (1) information was presented during adequate anaesthesia; (2) the hypnotic trance was not sufficiently deep; (3) the hypnotic interview technique was not appropriate (previous studies used ideomotor and non-verbal signalling as evidence of intraoperative memory[13–15]; (4) the reassurances given to the patients just before their hypnotic experience of anaesthesia may have implanted a suggestion that they would not be aware under anaesthesia and this implanted suggestion suppressed recall.

If adequate anaesthesia prevents encoding of auditorally presented material into long-term memory stores, then no amount of sophisticated psychological testing may extract the non-existent information.

In this study arm levitation was used as part of the technique for deepening the hypnotic state. There may be wide variations in susceptibility to hypnosis between subjects but, in general, those who attain arm levitation show substantially more hypnotic responsiveness than those who do not attain such levitation.[16] While lack of arm levitation does not necessarily imply that an individual subject is resistant to hypnosis, on average, such subjects obtain scores in the lower third of the Stanford hypnotic susceptibility scale (i.e. may be less responsive to hypnosis).[16] It seems unlikely that lack of an adequate depth of hypnotic trance was a cause for the absence of recall.

There is a suggestion that intraoperative instructions to perform a non-verbal response (e.g. touch your ear when you hear my voice again) may be a better indicator of recall for intraoperative information than verbal responses. Although the finger flexing response of the patient in whom the IFT cuff burst could be taken as evidence to support this view she was the only patient in the study to produce such a response and this followed exposure to a period when anaesthesia was known to be very light. Specifically designed studies of non-verbal responses have produced mixed results. Several of the investigations purporting to provide evidence for recall of suggestions for a non-verbal response had significant methodological or statistical inadequacies, or both, which makes interpretation of the results impossible.[4] There appears to be little conclusive evidence that suggestions for non-verbal behaviour during a postoperative interview are any more reliable than verbal responses as an indicator of recall for intraoperative information presented during general anaesthesia.

The reassurance given to the patients before their hypnotic experience of anaesthesia was felt to be important. Bennett suggests that intraoperative reminiscences can be powerful stimuli and should be approached with caution.[13] There would be little point in proceeding through the patient's anaesthetic experience under hypnosis only to find either that she "could not speak" (because of paralysis and intubation), "could not hear you" (because she was unconscious) and worst of all, stopped breathing (because of paralysis). While possible, it is unlikely that recall was impaired by the reassurances given during hypnosis before exploring intra-anaesthetic memory. Four of the five women with recall expressed their recall under hypnosis. Another woman, under hypnosis, was "gagging" on the tracheal tube and "pushing" against the ventilator as she emerged from "anaesthesia" and as the "tracheal tube was removed" she said, "God I feel crap". This was exactly the sequence of events and words used at the end of her real anaesthetic.

As in other studies,[13] this investigation provided clear evidence of confusion and fabrication when using hypnosis, thus emphasizing the importance of being able to verify the material claimed as recall. There were also other unforeseen problems which arose during hypnosis and it is as well that other investigators should be aware of these. The hypnotic sessions of nine women deviated from normal. These women all "broke down" and began crying at some stage during hypnosis. With the patient's permission the cause of the crying was investigated before continuing with the normal hypnotic interview. The most common reasons for crying were of a psychosexual nature: the woman's "wholeness" and "attractiveness" for future sexual relationships (five women); sexual abuse as a teenager by her father (one); and psychological/physical/sexual abuse by her husband (one). The two other causes of crying were an overwhelming fear of cancer (one) and fear of experiencing severe postoperative pain, as experienced after previous abdominal surgery (one).

The importance of direct assessment of a patient's conscious level during anaesthesia is emphasized by the lack of spontaneous movement from the three women with unequivocal evidence of recall for the time around the start of surgery: despite having a non-paralysed forearm none responded to skin incision. The unreliability of clinical monitoring is illustrated by the fact that only one of these three patients was suspected of being inadequately anaesthetized and this was confirmed by clear responses to command (see appendix).

Both premedication and neuromuscular blocking agents reduce the MAC value of inhalation anaesthetics and, taking these effects into account, it was estimated that the MAC value of the anaesthetic given was approximately 1.5 MAC. To assure surgical anaesthesia, a MAC value of 1.25–1.3 is recommended[17] but Cormack[18] stated that "With neuromuscular block, surgery can be carried out at less than 1 MAC, and this has proved satisfactory in millions of patients". In the absence of an end-tidal halothane concentration monitor in this study, it is impossible to estimate alveolar halothane concentration at the beginning of surgery but the anaesthetic was sufficient to prevent the perception of pain in all patients and only one woman (patient c) was aware of surgery (a painless skin incision). The times from induction to skin incision in the three women with recall for the start of surgery were 14 min (patient a), 12 min (patient b) and 5 min (patient c). These three epidoses emphasize the need for a higher concentration of volatile agent for the first few minutes of anaesthesia, particularly if no direct assessment of conscious levels is being made. Normal clinical signs do not ensure unconsciousness.

As with all negative results, the power of a study is important. Previous studies with a positive result using a similar methodology reported target words more often in the test group than in the control group: 2.4 *vs* 1.84,[19], 2.7 *vs* 0.9,[20] 1.5 *vs* 0.5.[21] A composite average response from analysis of these results suggests that our study had a power of 95% of detecting similar differences at the 0.05% level. While it is always possible that a type II error may have occurred, the responses of the two groups in this study were so similar that this seems unlikely.

In summary, there is no evidence from this investigation that women anaesthetized with nitrous oxide and halothane and who were unresponsive to commands at the time specific information was presented to them had either explicit or implicit memory for this information. Our results suggest that if intraoperative implicit learning occurred then it probably did so during episodes of inadequate anaesthesia. Further research in this area, if purporting to reflect an adequately anaesthetized state as opposed to some type of quasi-amnesia with paralysis, must include systematic, accurate and direct intraoperative monitoring of levels of consciousness with the IFT during the period when information is presented.

## Appendix

### DESCRIPTION OF EVENTS FOR PATIENTS WITH POSTOPERATIVE RECALL

*Table 4, patient "a": group RSG—no hypnosis*

This 95-kg patient was aware of someone opening her eyelid and I. F. R.'s voice asking her to do something. She found I. F. R.'s voice soothing and comforting. There was no pain, she was unaware of any other sensations and was not aware of skin incision. She then described the sudden onset of a buzzing noise which blocked everything out before she drifted off to sleep.

During the 10 min after intubation, while she was being prepared for abdominal hysterectomy, her pupils remained moderately dilated, she continued to produce tears, and heart rate and arterial pressure remained high. Despite her being assigned to the white sound group, the first author (I. F. R.) asked her directly to "squeeze my fingers". When she responded, which she did twice (at 6 min and 10 min) she was reassured everything was going well and she would soon be asleep. Thiopentone 100 mg was given on each occasion. At skin incision (14 min) she moved her hand reflexly but there was no response to direct command. No other commands were given. The white sound tape was switched on at 16 min. It is of some relevance that she had "a bad experience" during her second Caesarean section and after this she woke up crying and was "upset" for several days. The Caesarean section anaesthetic record was obtained subsequently from another hospital: this revealed the use of minimal doses of drugs, quite inadequate for a 100-kg patient (thiopentone 250 mg and 50% nitrous oxide only before delivery; 63% nitrous oxide, fentanyl 100 µg and 0.2% trilene after delivery). It seems likely that she had been awake during that Caesarean section but had no conscious recall of the events Unfortunately, she did not give consent for hypnosis so further investigation of her Caesarean section experience was not possible. Details of this "bad experience" did not emerge during the preoperative interview!

During her postoperative interviews she responded with "pear" in recovery and on day 3, in third and fourth positions, respectively.

*Table 4, patient "b": group RSG—hypnosis*

This patient was aware of female voices asking someone to "pass something" when the sudden onset of a buzzing noise prevented her from hearing anything else before she went to sleep. There was no pain. It is more than likely that this patient heard the surgical team during preparations for vaginal hysterectomy and then the white noise masked everything. She was unaware of surgery. There were no responses of any type from the isolated arm.

During the postoperative interviews she did not reply with any target fruits, either in recovery or on day 3.

*Table 4, patient "c": group CG—hypnosis*

This patient, undergoing abdominal hysterectomy, claims to have heard talking, to have been aware of people "at the bottom" and was aware of skin incision. There was no pain and she drifted off to sleep before she could become anxious. There were no responses of any type from the isolated arm.

During postoperative interviews she gave no target fruits in recovery but in the word association test responded to "sour" with "lemon". On day 3 she gave "pear" in fifth position and responded to "sour" with "grapefruit".

*Table 4, patient "d": group CG—hypnosis*

This patient undergoing vaginal hysterectomy was aware of someone "doing things to her down there, things she did not like". Because of this she felt she was a "dirty person".

This patient had a very poor body image and regarded anything to do with genitalia as "dirty". After the tape was switched off and halothane was discontinued she woke up very quickly as the surgeon was placing a vaginal pack.

In recovery she gave "lemon" in first position. On day 3 she gave lemon in third position.

*Table 4, patient "e": group CG—hypnosis*

During hypnosis this patient claimed to have been aware of talking. She does not know when, or what was said. She felt the colour "green" had particular significance. On emerging from hypnosis she was opening and closing the fingers of her right hand. When asked why she was doing this she said that she wanted to "straighten and relax her fingers" while hypnotized but had been unable to do so. She was sure she had been asked to do something with her fingers.

Under anaesthesia for abdominal hysterectomy there were six reflex responses of the isolated forearm over the first 15 min of surgery. There was no other clinical evidence of light anaesthesia and no response to command. At 16 min the cuff was inflated and atracurium 20 mg administered. The arm remained unparalysed and there were no further movements. However, 10 min after this second dose of atracurium the IFT cuff burst and the right arm became paralysed, remaining so until the end of surgery. The command tape continued playing during this time. At the end of surgery while her trachea was being extubated the surgeon made several loud comments regarding the "green swabs" used by anaesthetists in this hospital.

In recovery she was too sedated to respond adequately and only a single response was obtained. This was in the word pair test: she promptly gave "swab" to the cue word "green". On day 3 under hypnosis she responded with "lemon" in first position and pear in fourth position. In the word association test she emphasized the importance of green but did not know why this colour should have such a special significance. In the word association test she responded to "green" with both "emerald" and "tree".

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# Extradural morphine gives better pain relief than patient-controlled i.v. morphine after hysterectomy

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## Summary

We examined if patient-controlled analgesia (PCA) with i.v. morphine provided comparable postoperative analgesia after hysterectomy as extradural morphine, without increasing the incidence of side effects. The study ($n$=40) was randomized and double-blind. An extradural catheter was inserted before surgery and anaesthesia was standardized. The extradural group received extradural morphine 0.06 mg kg$^{-1}$ by the end of surgery and a second dose 6 h later. The i.v. group received an i.v. infusion of morphine 0.2 mg kg$^{-1}$ after surgery. PCA with morphine 0.04 mg kg$^{-1}$ i.v. was used in both groups. Pain relief (VAS), side effects and cognitive functions were evaluated for 18 h. Plasma samples were obtained for analysis of morphine concentrations. Mean consumption of PCA morphine was 2.4 mg h$^{-1}$ for the i.v. group and 1 mg h$^{-1}$ for the extradural group. Despite unlimited access to morphine, the i.v. group had higher VAS scores as the extradural group ($P$<0.001). Plasma concentrations of morphine varied 8–10-fold in both groups. In the i.v. group itching, tiredness, blurred vision and vertigo correlated with cumulative consumption of i.v. morphine whereas in the extradural group this correlation existed only for tiredness. Both groups showed reduced ability to perform tests of cognitive function; indicating a central effect of both i.v. and extradural morphine, despite markedly lower plasma morphine concentrations in the extradural group. (*Br. J. Anaesth.* 1997; **78**: 10–16)

**Key words**
Analgesia, postoperative. Analgesics opioid, morphine. Analgesia, patient-controlled. Anaesthetic techniques, extradural.

A single dose of extradural morphine provides better and longer lasting pain relief after major surgery than a single dose of i.v. or i.m. morphine.[1–3] However, the clinical use of extradural morphine is hampered by side effects such as pruritus, vomiting, delayed gastric emptying and, most importantly, respiratory depression.[4] Respiratory depression usually occurs within 12 h, although it may occur later, up to 24 h after administration of extradural morphine.[1 2 4] This delay necessitates supervision of patients for 12–24 h[4]. I.v. morphine can also produce respiratory depression.[5]

It is well known that the need for i.v. opioids in the postoperative period varies between patients undergoing similar types of surgery even though the same anaesthetic techniques are used.[6] In the postoperative period, patient-controlled analgesia (PCA) is a valuable method for providing pain relief.[5–7] The PCA device allows patients to administer i.v. opioids according to individual needs. Consequently, after major surgery it may be possible to evaluate if the consumption of i.v. morphine gives equivalent or superior pain relief compared with single doses of extradural morphine. This has been examined in some controlled studies with contradictory results.[7–10]

Loper and Ready found that patients given repeated doses of extradural morphine after arthrotomy reported significantly lower pain scores than those using PCA with i.v. morphine.[10] In contrast, Weller and co-workers[7] could not find any significant differences in pain ratings between patients receiving single doses of morphine by the extradural route and those who received i.v. morphine using PCA after orthopaedic surgery. A third study reported that after Caesarean section, extradural morphine gave superior pain relief than PCA with i.v. morphine.[8] In that study, the PCA doses were 1–2 mg and the lockout time was 6 min.[8] The low doses may have reduced the full potential of the PCA technique.

Plasma concentrations of morphine and their relation to reported side effects are seldom investigated after i.v. and extradural administration in the postoperative period. We have found no study comparing the efficacy of repeated doses of extradural morphine with higher doses (2–4 mg) of i.v. morphine administered by PCA. In this study, we have compared the effects of PCA administration of i.v. morphine with extradural morphine during the initial 18 h after hysterectomy. The first hypothesis was: patient-controlled administration of i.v. morphine with an initial bolus dose of i.v. morphine can

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give as good or better pain relief as single doses of extradural morphine combined with PCA administration of i.v. morphine. The second hypothesis was: PCA i.v. morphine administration does not result in more side effects than extradural morphine.

## Patients and methods

The study was approved by the Huddinge Hospital Ethics Committee. The study was double-blind and patients were allocated randomly to one of two groups: i.v. or extradural (table 1).

### PATIENT RECRUITMENT

We examine 84 consecutive patients undergoing elective hysterectomy (table 2). Exclusion criteria included backache, obesity, psychiatric disease and age more than 60 yr. Five patients who had agreed to join the study were not included because of administrative problems such as lack of beds in the post-operative unit. We calculated body mass index (BMI, weight (kg) divided by height$^2$ (m)) and considered $<25$ kg m$^{-2}$ to be normal.[11] Patients with a BMI value less than 32 kg m$^{-2}$ were accepted. We studied 40 female patients who fulfilled the inclusion and exclusion criteria.

All patients met the anaesthetist (M. E.-M.) the day before surgery and were given full verbal and written information on the study. They were instructed on how to use the visual analogue scale (VAS) for pain rating and the PCA device was demonstrated. We also performed baseline cognitive tests (see neuropsychological assessments), blood-gas analysis of arterial blood, and venous blood samples were obtained as a zero reference for plasma concentrations of morphine.

### ANAESTHESIA AND SURGICAL PROCEDURES

The anaesthetic procedure was standardized. Patients were given diazepam 10 mg orally in the ward, 1 h before the start of anaesthesia. All patients had an extradural catheter inserted at lumbar segments L3–L4 or L2–L3. Mepivacaine 20 mg ml$^{-1}$ with adrenaline was given extradurally as two consecutive doses. After a test dose of 3 ml, another 12 ml were given to women younger than 50 yr and 9 ml to women older than 50 yr. When the anaesthetic level for pinprick reached T10–12, patients were anaesthetized with thiopentone 5 mg/kg body weight and fentanyl 0.2 mg. After pancuronium 1 mg, intubation was facilitated with suxamethonium 1 mg/kg body weight. Isoflurane 0.5% was given in a mixture of nitrous oxide and oxygen to maintain anaesthesia. A single dose of pancuronium 3 mg was given before the start of surgery and additional 1-mg doses when needed. A top-up dose of mepivacaine 8 ml with adrenaline 10 mg ml$^{-1}$ was given during surgery, 1 h after the first dose.

*Table 2* Patient recruitment

| | | |
|---|---|---|
| Considered for enrolment | 84 patients | |
| Refused extradural anaesthesia | 10 | |
| Administrative problems | 5 | |
| Excluded | 29 | |
| History of: | | |
| Back pain | | 15 |
| Psychiatric disease | | 2 |
| Easily induced vomiting after opioid administration | | 2 |
| High body mass index | | 5 |
| Poor fluency in Swedish | | 5 |
| Included in study | 40 | |

Administration of isoflurane was discontinued when the skin was closed, and neuromuscular block was antagonized with neostigmine 2.5 mg.

All patients underwent abdominal hysterectomy with or without salpingo-oophorectomy via a Pfannenstiel incision (39 patients). A midline incision was used in one patient only.

### STUDY DESIGN

Blinded solutions of extradural and i.v. morphine, and saline were prepared by the hospital pharmacy and stored in glass bottles. At closure of the peritoneum, patients in the extradural group received a single dose of extradural morphine 0.4 mg ml$^{-1}$, corresponding to 0.06 mg/kg body weight (table 1). The mean dose given was 4 (SD 0.5) mg. Patients in the i.v. group received the same volume of 0.9% saline.

After surgery patients were awakened and the trachea extubated. After a mean time of 15 min after the end of surgery, patients were brought to the recovery room where they were monitored for a minimum of 18 h. On arrival in the recovery room (time 0) patients in the i.v. group received an i.v. infusion of morphine 0.2 ml/kg body weight over 20 min. Mean dose was 12.4 (range 10.2–17.6) mg. Patients in the extradural group received the same i.v. volume of physiological saline solution.

Patients were connected to the PCA device (Prominject, Pharmacia) which was set to deliver a bolus dose of i.v. morphine 0.04 mg/kg body weight whenever the patient pushed the button. The amount of morphine given in a single dose varied from 2–3.5 mg. A lockout time of 10 min was used.

*Table 1* Design of the study

| | I v. group | Extradural group |
|---|---|---|
| 1 | Extradural NaCl 0.15 ml kg$^{-1}$ as bolus dose when peritoneum is closed | Extradural morphine 0 15 ml kg$^{-1}$ (0 06 mg kg$^{-1}$) as bolus dose when peritoneum is closed |
| 2 | Intravenous morphine 0.2 ml kg$^{-1}$ (0.2 ml kg$^{-1}$) after awakening | I v. NaCl 0.2 ml kg$^{-1}$ after awakening |
| 3 | PCA 0.04 mg kg$^{-1}$ bolus dose. Lockout time 10 min | PCA 0.04 mg kg$^{-1}$ bolus dose. Lockout time 10 min |
| 4 | Extradural NaCl 0.15 ml kg$^{-1}$ 6 h after first dose | Extradural morphine 0.15 ml kg$^{-1}$ (0.06 mg kg$^{-1}$) 6 h after first dose |

A second dose of extradural morphine 0.06 mg/kg body weight was given 6 h after the initial dose, and a blinded dose of extradural saline to the i.v. group. The mean cumulative dose of extradural morphine after the second dose was 7.9 (1.2) mg.

Plasma samples were obtained and pain ratings were assessed before the first three episodes of self-administration. These usually occurred during the first 2 h after arrival in the recovery room. Postoperative pain was assessed using a 100-mm visual analogue scale (VAS) where 0=no pain and 100=unbearable pain. Additionally, VAS scores were assessed and arterial blood samples obtained at specific times (0, 0.5, 1, 2, 4, 8, 12 and 18 h, and at 1, 2, 4, 8 and 18 h, respectively, after arrival in the recovery room). Patients spent the night in the recovery room where mobilization is not routine. To evaluate the effects of i.v. and extradural morphine, frequent VAS measurements were made and evaluation of side effects and influence on cognitive functions. VAS assessment on movement and during coughing were not measured as the patients were not mobile.

### ASSESSMENT OF ADVERSE EVENTS

At 4, 8 and 18 h after arrival in the recovery room, staff asked the patients if they experienced any adverse events. If so, they were questioned specifically about the presence of nausea, vomiting, tiredness, vertigo, dry mouth, pruritus, blurred vision and dyspnoea. They were asked to grade symptoms from 0 to 3, where 0=no symptoms, 1=mild, 2=moderate and 3=severe.

### COGNITIVE FUNCTIONS

Two tests of cognitive function were used: the grammatical reasoning test[12] and the letter cancellation test.[13] The grammatical reasoning test evaluates reasoning ability and the letter cancellation test assesses visual search ability, which is measured by speed (number of items covered in 3 min) and correctness (percentage correct) of responses. Both tests were presented to all subjects on four occasions: 1 day before surgery and at 2, 8, and 18 h after arrival in the postoperative unit. The ability to perform both tests varied considerably as a result of incapacity (tiredness), which might be evaluated by compliance rate (percentage of individuals making efforts to solve the tests).

### CLINICAL CARE

We monitored heart rate, systolic and diastolic arterial pressures, and ventilatory frequency every 30 min. Arterial blood-gas tensions were measured at 2, 8 and 18 h after arrival in the recovery room. Patients were given i.v. glucose and balanced electrolyte solutions, approximately 2–3 litre, over 18 h.

### ANALYTICAL METHODS

Blood samples were centrifuged within 1 h. Plasma was transferred into plastic tubes and stored at −20°C until analysis. Plasma concentrations of morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) were assayed in duplicate using high pressure liquid chromatography, as described previously.[14] The method has an STD (inter-day) variability of 7.0%, 4.2% and 3.3% when assaying plasma concentrations of morphine, M3G and M6G, respectively, at therapeutic concentrations. The area under the plasma morphine concentrations *vs* time curve (AUC) (0–18 h) was calculated for each individual.

### STATISTICAL METHODS

The results were tested with Student's *t* test for parametric data and the Mann–Whitney *U* test for non-parametric data. Results are given as mean (SD) or median (range) according to distribution. For repeated measurements the Friedman test was used. For analysis of correlation the Spearman rank test was used. $P<0.05$ was considered significant. The possible differential deleterious effects on cognitive function from the two methods of postoperative pain relief were analysed using a 2 (groups) × 4 (test occasions) ANOVA for each measure.

## Results

There were no differences in age, weight, height or duration of surgery between the groups (table 3). There was a difference in BMI ($P<0.05$) and in perioperative bleeding ($P<0.05$). There were three patients with excessive bleeding. One patient in the i.v. group bled 2100 ml and two patients in the extradural group bled 1400 ml and 1500 ml, respectively. One patient in the i.v. group and six patients of those receiving extradural morphine bled 500–1000 ml. All other patients lost less than 500 ml.

Patients in the extradural group reported lower pain scores than the i.v. group at 4, 8, 12 and 18 h after arrival in the postoperative unit ($P<0.001$) (fig. 1). At 4 and 18 h, mean VAS scores were 9 (SD 11) mm and 9 (13) mm, respectively, in the extradural group. Corresponding values in the i.v. group were 51 (23) mm and 28 (18) mm, respectively. Even though extradural morphine was administered on average 30 min before arrival in the postoperative unit, these patients had as high VAS scores as women treated with i.v. morphine during the initial 1 h (fig. 1). Patients reported no pain on awakening. At 8 h, only two of 20 patients in the i.v. group were pain free (VAS=0) compared with 15 of 20 patients

*Table 3* Characteristics of patients (mean (SD) or range). $^*P<0.05$

| | I.v. ($n$=20) | Extradural group ($n$=20) |
|---|---|---|
| Age (yr) | 45 (32–52) | 46 (36–56) |
| Weight (kg) | 63 (11) | 67 (8) |
| BMI (kg m$^{-2}$) | 23 (3) | 25 (3)* |
| Surgery (min) | 105 (31) | 107 (37) |
| Bleeding (ml) | 368 (430) | 520 (390)* |
| Mepivacaine (mg) | 378 (14) | 378 (14) |

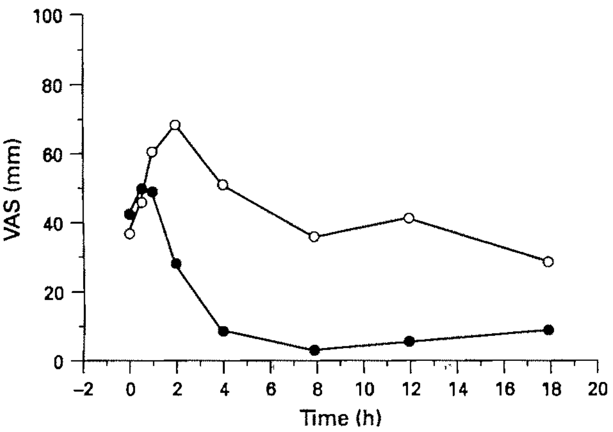

*Figure 1* Mean pain scores (VAS) in the extradural (●, $n=20$) and i.v. (○, $n=20$) morphine groups during the initial 18 h after operation. Time 0=time of arrival in the recovery room.

in the extradural group. The corresponding values at 18 h were two of 20 and 10 of 20, respectively.

There was a difference between groups in the frequency and timing of demand for PCA morphine (fig. 2). The extradural group took only a few doses (mean 6.6 (5.9) (range 0–23) doses) (fig. 2), mostly within 2 h. The i.v. group took morphine repeatedly over 18 h (mean 18 (7.3) (range 7–30) doses) (fig. 2). This difference was significant ($P<0.001$, Mann–Whitney). Consequently, the cumulative dose of morphine at the end of the 18-h study period differed between the two groups (fig. 3). The cumulative dose was 14–105 mg in the i.v. group and 0–55 mg in the extradural group ($P<0.001$, Mann–Whitney). Mean morphine consumption in the i.v. group was 44 (20.8) mg corresponding to 2.4 mg $h^{-1}$ over 18 h. The values were 17.2 (16) mg and 1 mg $h^{-1}$ for the extradural group (fig. 3).

In the i.v. group we found a 10–20-fold variability in plasma morphine concentrations when patients took their three initial i.v. bolus doses of PCA morphine (table 4). Plasma concentrations of M6G before the first, second and third PCA doses showed less variation but increased significantly with time ($P<0.001$, Friedman test) (table 4). Plasma concentrations of morphine in the extradural group were markedly lower at the initial three PCA doses. Interestingly, mean plasma morphine concentrations, before the initial three doses, were consistent in patients in the i.v. group. Plasma concentrations of morphine at fixed intervals in the two groups are presented in figure 4. Concentrations were highest at 1 and 2 h when pain scores were high. There were large inter-individual variations in plasma concentra-

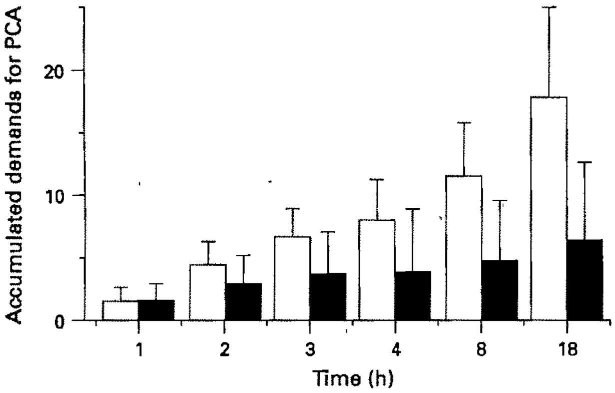

*Figure 2* Accumulated successive demands for PCA in the extradural (■, $n=20$) and i.v. (□, $n=20$) groups during the 18 h after operation. Values are mean, SD.

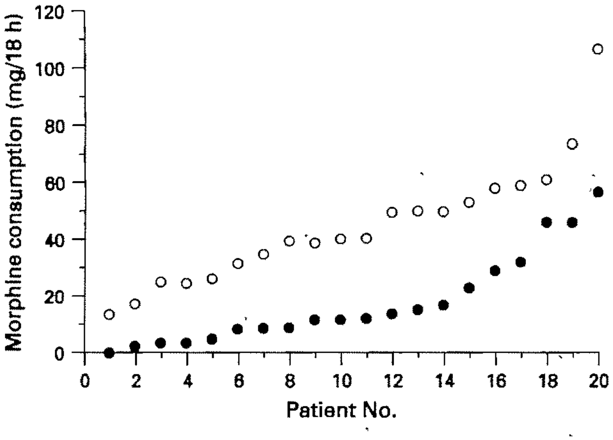

*Figure 3* Cumulative PCA morphine consumption over 18 h in individual patients in the extradural (●) and i.v. (○) groups ($n=20$ patients in each group), ranging from the lowest to the highest morphine consumption.

*Table 4* Plasma morphine and morphine-6-glucuronide (M6G) concentrations and pain ratings in the i.v. and extradural groups before self-administration of i.v. morphine (mean (SD) (range)). ***$P<0.001$ (Friedman test)

| | Before 1st PCA dose | Before 2nd PCA dose | Before 3rd PCA dose |
|---|---|---|---|
| VAS | | | |
| I.v group | 70 (21)<br>(25–100) | 71 (21)<br>(30–100) | 73 (24)<br>(38–100) |
| Extradural group | 57 (32)<br>(0–100) | 67 (22)<br>(30–100) | 63 (26)<br>(26–100) |
| Plasma morphine concentration (nmol litre$^{-1}$) | | | |
| I.v. group | 169 (158)<br>(29–637) | 130 (113)<br>(45–529) | 108 (62)<br>(40–309) |
| Extradural group | 19 (9.9)<br>(0–32) | 52 (46)<br>(2.7–167) | 67 (43)<br>(8–155) |
| Plasma M6G concentration (nmol litre$^{-1}$) | | | |
| I.v. group | 100 (37)<br>(11–168) | 149 (46)<br>(69–256) | 162 (40)***<br>(78–235) |
| Extradural group | 19 (8.3)<br>(0–34) | 31 (19)<br>(1.7–68) | 58 (29)<br>(14–94) |

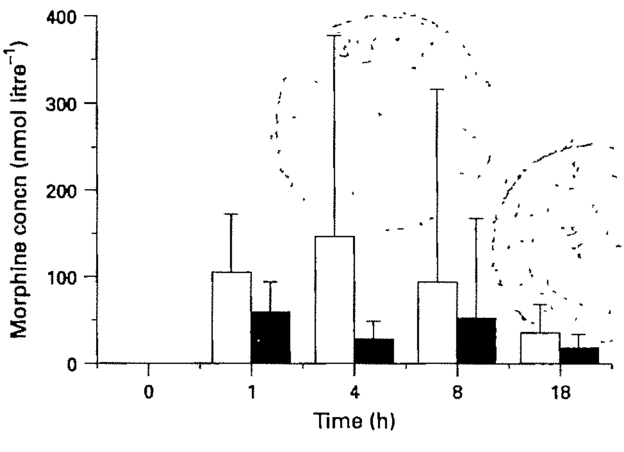

*Figure 4* Plasma concentrations of morphine at 1, 4, 8 and 18 h in the extradural (■, $n=20$) and i.v. (□, $n=20$) groups. Values are mean, SD

tions, especially in the i.v. group. Morphine concentrations were lower in the extradural group during the whole postoperative period, resulting in mean 18 h AUC values of 1504 (2106) (range 172–9977) nmol h for the i.v. and 497 (577) (range 97–2591) nmol h for the extradural group, respectively ($P<0.001$, Mann–Whitney). We found no correlation between AUC of plasma morphine concentrations and the AUC of VAS in either group over 18 h or any correlation between cumulative consumption of morphine at 18 h and AUC of VAS at 0–18 h.

### SIDE EFFECTS

All patients in each group reported adverse events. Tiredness and dryness of the mouth were frequent in both groups of patients. At 2 and 8 h, all patients in the i.v. group reported mild to severe tiredness and at 18 h only one patient reported no tiredness. In the extradural group ($n=20$), 16–17 patients reported mild to severe tiredness at 2, 8 and 18 h. At 18 h the frequency of itching was 24% and 37% in the extradural and i.v. groups, respectively (ns). The risk of morphine-induced urinary retention could not be measured as all patients had urinary catheters for more than 24 h.

At 18 h after arrival in the recovery room (time 0), cumulative PCA morphine in the i.v. group correlated with intensity of each of the following side effects: tiredness, itching, blurred vision and vertigo ($n=20$ , $P<0.05$ Spearman rank; 0=no symptoms, 1=mild, 2=moderate and 3=severe). In the extradural group tiredness at 18 h correlated with cumulative morphine ($n=20$ , $P<0.05$, Spearman rank). Preoperative $Pa_{CO_2}$ was less than 5 kPa in both groups. At 8 h, mean $Pa_{CO_2}$ was 5.7 kPa in the extradural and 5.6 kPa in the i.v. group, with similar variability within each group. Both groups had a significantly increased $Pa_{CO_2}$ compared with preoperative values ($P<0.001$, Friedman test), but there was no difference between groups (Mann–Whitney).

One patient in the extradural group experienced respiratory depression with increasing $Pa_{CO_2}$ levels up to a maximum of 8.3 kPA at 10 h after the first dose of extradural morphine and 4 h after the second extradural dose. A total of 7.32 mg of extradural morphine had been given to this patient. She had self-administered i.v. morphine on two occasions and had received a total dose of 4.8 mg of i.v. morphine at 10 h. This patient also hypoventilated with decreasing ventilatory frequency but had no signs of apnoea. Her ventilatory frequency was less than 10 bpm on several occasions, but she did not require ventilatory support and administration of naloxone was not necessary.

### COGNITIVE FUNCTIONS

Some patients were too tired to complete the tests (compliance). At 2 h after arrival in the recovery room, 45% in the extradural and 70% in the i.v. group were too tired to complete the tests. The effect of group was not statistically significant for any of the cognitive measures or compliance. But the effect of test occasion was significant for both compliance ($P<0.0001$), speed ($P<0.0001$) and correctness ($P<0.05$) of letter cancellation and for compliance ($P<0.0001$) and correctness of grammatical reasoning ($P<0.001$), but not for speed of grammatical reasoning. There was no interaction between group and test occasion in any measure. There were no significant differences between groups.

### CLINICAL CARE

There were no differences between the extradural and i.v. groups in arterial pressure, heart rate or ventilatory frequency. In both groups several patients had a ventilatory frequency less than 10 bpm but no patient had apnoea.

## Discussion

Our results confirm previous reports on excellent postoperative analgesia from extradural morphine, and support the opinion that the quality of pain relief from extradural morphine is superior to that generated by i.v. morphine administered on demand by patients.[1 9 10 15]

Two doses of extradural morphine gave very good analgesia. During the 18 h after operation, only eight of 20 patients required more than 15 mg of i.v. PCA morphine. However, four of 20 patients required more than 30 mg of i.v. PCA morphine in addition to extradural morphine. Sjöström, Hartvig and Tamsen[16] have shown that a minority of patients take remarkably high PCA doses of extradural morphine in the postoperative period. In their study, hourly consumption of extradural morphine via PCA varied from 0.19 to 1.04 mg. It is not yet known what mechanisms are behind this variability among patients in the need for opioids after extradural morphine administration. During the first 1–2 h in the recovery room, patients in the extradural group had VAS scores of 30–40 mm (fig. 1). The slow onset of analgesia in the extradural group was related to the hydrophilic nature of morphine causing slow diffusion of drug to the site of opioid receptors localized in the dorsal horn of the spinal cord.[2 17]

Despite individualized administration of i.v. morphine, patients in the i.v. group had consistently higher VAS ratings than the extradural group. It seems unlikely that they could have taken more morphine as all patients except one complained of tiredness. A few patients hesitated to use additional PCA doses because of fear of side effects such as vomiting and nausea. This fear proved correct as we found an association between high doses of i.v. opioids and side effects. An infusion longer than 1 min was not feasible to reduce side effects as some patients complained of incomplete pain relief from PCA, especially during the first 2 h after surgery. These patients, in contrast, found the lockout time of 10 min too long. Nevertheless, the i.v. group had mean VAS scores greater than 30 mm during the whole postoperative period. In spite of the i.v. loading dose and our relatively high PCA doses, pain relief was inadequate.

Why did i.v. morphine provide unsatisfactory pain relief after hysterectomy in this study? It has been suggested that various forms of pain (or pain components) are differentially sensitive to the route of administration of opioids. In one study, patients with visceral pain that was inadequately relieved by systemic opioids had pain relief from extradural morphine.[18] As hysterectomy is an abdominal operation there is a somatic (cutaneous and muscular) and a visceral pain component. I.v. morphine and i.v. pethidine had little effect on the visceral components of labour pain whereas the somatic type (back pain) was relieved.[19 20] We suggest that failure of i.v. morphine to provide as good analgesia as extradural morphine can be explained by the fact that i.v. opioids are less efficient in treating visceral pain.[19 20]

We found nine-fold variation in the amount of self administered morphine in the i.v. group over the 18 h after operation. This variation is in accord with results reported by previous investigators.[6 21] Patients in the i.v. group required a mean of 2.4 mg $\text{h}^{-1}$ of morphine. This value is close to that of 2.6 mg $\text{h}^{-1}$ reported by Tamsen and colleagues in middle-aged patients (30–50 yr) undergoing major colon surgery.[5] We also observed marked inter-individual variability in plasma morphine concentrations (more than 10-fold). Mean plasma morphine concentrations decreased slightly from the first to the third self-administered dose (ns). Our results indicate that there are inter-individual differences in sensitivity to morphine. The reason is unknown but could be genetically influenced. There was a significant increase in concentrations of M6G which could explain the decreasing concentrations of mean plasma morphine as M6G contributes to pain relief.[22] The highest plasma concentrations of morphine were seen at 1 and 4 h when VAS scores were high (figs 1, 4).

Even when patients in the i.v. group had high concentrations of morphine (mean 169 nmol $\text{litre}^{-1}$ before the first PCA dose) their pain relief was inadequate (table 4). Dahlström and co-workers estimated 16 ng $\text{ml}^{-1}$ ( equivalent to 56 nmol $\text{litre}^{-1}$) as the minimum analgesic concentration.[6] This value was not confirmed in our investigation where patients had high pain scores even at morphine concentrations greater than 56 nmol $\text{litre}^{-1}$ (table 4). The AUC of morphine concentrations 0–18 h did not correlate with the AUC of VAS, indicating that plasma morphine concentration was not directly influencing the extent of pain relief. Morphine concentrations at 1, 4 , 8 and 18 h, and the AUC of morphine concentrations 0–18 h were significantly lower in the extradural group who nevertheless had superior pain relief. This result is in accord with earlier studies showing that the pain relief from extradural morphine is mainly caused by its effect on receptors in the spinal cord[2] while plasma morphine concentrations are more important for side effects and influence on cognitive functions.[17] Unexpectedly, no differences in cognitive functions were seen between the groups. Cognitive tests for monitoring CNS effects indicated that all patients were affected, especially at 2 h after operation, showing that the tests were sensitive.

There are few studies showing VAS scores within 1 h of awakening after abdominal surgery. In an investigation of pain relief after hysterectomy, VAS scores were 65 mm (mean) in the control group immediately after surgery.[23] There are other studies where VAS scores were 50–65 mm during the first 2 h after surgery.[24–26] We have found no study on abdominal surgery showing VAS scores less than 40 in this early period when parenteral opioids are used for pain relief. These results are similar to ours and suggest that extradural morphine or local anaesthetics have to be administered in advance and before the end of surgery.

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# Target-controlled infusion of alfentanil for postoperative analgesia: a feasibility study and pharmacodynamic evaluation in the early postoperative period

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**Summary**

We have examined the feasibility of target-controlled infusion of alfentanil (TCIA) and the pharmacodynamics of alfentanil in the early postoperative period. Patients were allocated randomly to one of the three groups to receive balanced anaesthesia with bolus injections of fentanyl (group F), sufentanil (group S) or alfentanil (group A. In the recovery room all patients received the same analgesic regimen, comprising TCIA. To evaluate the efficacy of postoperative analgesia, pain scores were measured on a visual analogue scale (VAS) and patients indicated a need for additional analgesia. EC$_{50}$, the concentration at which, with a 50% probability, patients reported adequate analgesia, was estimated using logistic regression. Six patients did not complain of pain. The time from the last intraoperative bolus injection of opioid until patients complained of postoperative pain was shorter ($P<0.05$) in group A (mean 68 min) than in group F (101 min) and group S (136 min). The time to onset of satisfactory analgesia was comparable in the three groups (median 18 min in group F, 15 min in group S and 14 min in group A). EC$_{50}$ of alfentanil was determined in 28 patients; mean values were 26 ng ml$^{-1}$ (group F), 39 ng ml$^{-1}$ (group S) and 52 ng ml$^{-1}$ (group A). We conclude that TCIA, under the conditions studied, resulted in a fast onset of adequate analgesia, irrespective of the opioid administered during operation. Also, there was no effect of opioids administered during operation on postoperative pharmacodynamics of alfentanil. (*Br. J. Anaesth.* 1997; **78**: 17–23)

**Key words**

Analgesia, postoperative Analgesia, target-controlled. Analgesics opioid, alfentanil. Pain, postoperative Pharmacodynamics, alfentanil. Pharmacokinetics, alfentanil.

The pharmacological properties of alfentanil (fast onset of action, fast distribution and elimination) make this opioid suitable for use in the postoperative period. Alfentanil is administered preferably by continuous i.v. infusion, whereby after operation the infusion rate is adjusted to the patient's requirements. Alfentanil has been used successfully after operation when administered to the patient by a target-controlled infusion (TCI) system.[1-3] A thorough understanding of the pharmacokinetics and pharmacodynamics of the drug used is essential for rational administration of an analgesic by TCI. Previous studies[4-6] have shown that the pharmacokinetics of alfentanil, studied before and after operation, are applicable when implemented in a TCI system used for prolonged postoperative administration.

Previous studies[1 6] using TCIA have been conducted under strictly standardized conditions for surgery and intraoperative medication. The aim of this study was to investigate the feasibility of the TCI system in the early postoperative phase after balanced anaesthesia with different opioids in a wide patient population.

The pharmacodynamics of alfentanil have only been studied using the minimum effective analgesic concentration in the postoperative period. In this study we evaluated the pharmacodynamics of alfentanil in the early postoperative phase. To study the pharmacodynamics of alfentanil we determined the EC$_{50}$, that is the concentration of alfentanil at which, with 50% probability, the patient reported adequate analgesia, using logistic regression, an approach that has been described to define the intraoperative concentration–effect relationships of various opioids. In addition, we examined the predictive performance of the TCI system, implemented with population pharmacokinetic data.[7]

## Patients and methods

After obtaining medical Ethics Committee approval and informed consent, we studied 37 patients, ASA I or II, aged 18–65 yr, undergoing elective general, major orthopaedic or gynaecological surgery under general anaesthesia lasting longer than 1 h. Patients

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with a history of cardiovascular, pulmonary, hepatic or renal disease and patients who had taken opioids in the preceding month were excluded. Patients were allocated randomly to one of three groups. All patients received a TCI of alfentanil for postoperative pain management. Before surgery each patient was instructed on the use of the system and on the use of the visual analogue scale (VAS) for pain scoring.

Premedication comprised temazepam 0.3 mg $kg^{-1}$ orally to the nearest 10 mg, 1 h before surgery. On arrival in the operating room, electrocardiogram electrodes were attached and arterial pressure measured. A cannula was inserted in a large forearm vein. After induction of anaesthesia, a 20-gauge cannula was introduced into a radial artery for arterial pressure monitoring and collection of blood samples. Anaesthesia was maintained with 66% nitrous oxide in oxygen and enflurane (end-tidal concentration 0.2–1.0 %) or isoflurane (end-tidal concentration 0.3–1.0 %). Anaesthesia was supplemented with bolus doses of fentanyl in patients in group F, with bolus doses of sufentanil in patients in group S and with bolus doses of alfentanil in patients in group A. The size of the bolus doses and the timing of intraoperative opioid injections were determined by the responsible anaesthetist, who was not involved in the postoperative part of the study. Bolus dose sizes and times of administration were noted. Pancuronium was given for neuromuscular block. At the end of surgery, the trachea was extubated after the patient had recovered consciousness and when adequate ventilation (ventilatory frequency $>8$ bpm, end-tidal carbon dioxide concentration $<6.5$ vol% and tidal volume $>7$ ml $kg^{-1}$) had been established. After extubation of the trachea the patient was transported to the post-anaesthesia care unit and supplementary oxygen was given routinely.

After operation all patients received the TCI system, which was connected to an i.v. cannula in a large forearm vein. The syringe contained alfentanil 0.25 mg $ml^{-1}$. A computer-controlled infusion pump was used for administration of alfentanil. The computer (Atari Portfolio, Acoustic, Japan) was connected to a syringe pump (Ohmeda 9000, Strector, UK) via a serial RS232 communication channel. The software, written in Pascal by one of the authors, was supplied with population pharmacokinetic data, reported by Maitre and colleagues.[7] The system allowed a theoretical target plasma concentration of alfentanil ($C_T$) to be attained rapidly and maintained. To achieve and maintain $C_T$, the infusion rate was recalculated and changed every 10 s by the computer. Cumulative volumes infused were stored at least every 1 min on a 128 Kb Portfolio memory card and with every change in $C_T$. For safety reasons the maximum infusion rate of the Ohmeda pump was limited to 100 ml $h^{-1}$ (=25 mg $h^{-1}$).

The patient was instructed to report the onset of pain to one of the investigators. At that moment the patient's pain was scored, using a 10-cm VAS, and the degree of sedation was scored using the six-point scale described by Ramsay and colleagues[8]: (1) patient anxious and agitated or restless, or both; (2) patient cooperative, oriented and tranquil; (3) patient responds to commands only; (4) patient asleep, but with a brisk response to a light glabellar tap or loud auditory stimulus; (5) patient asleep, sluggish response to a light glabellar tap or loud auditory stimulus; and (6) asleep, no response.

If the sedation score was $<3$, the TCI system was activated. The initial $C_T$ of alfentanil was 20 ng $ml^{-1}$. After 5 min the patient's sedation and pain scores were assessed and when the patient indicated a need for additional analgesia and the sedation score was $<3$, $C_T$ was increased by 10 ng $ml^{-1}$. These assessments and adjustments were repeated at 5-min intervals until the patient, while oriented (sedation score $<3$), indicated no need for additional analgesia, and had a VAS score $\leqslant 3.0$. When these criteria were met $C_T$ was maintained at the corresponding level. The loading period was ended when the oriented patient requested no additional analgesia, had a VAS score $\leqslant 3.0$ and $C_T$ had not been changed for 30 min. Thereafter, the step size in $C_T$ was decreased to 5 ng $ml^{-1}$ with a lockout period of 5 min.

If the patient did not request additional analgesia during a 10-min period $C_T$ of the computer-controlled infusion was decreased by 5 ng $ml^{-1}$. If 10 min after the new $C_T$ had been reached the patient still had not requested additional analgesia, $C_T$ was again decreased by 5 ng $ml^{-1}$. This procedure was repeated until a request for additional analgesia was made, when $C_T$ was increased by 5 ng $ml^{-1}$, as described above.

Every 5 min VAS score, sedation score and vital signs were documented. No VAS scores were obtained when the patient was asleep. Peripheral oxygen saturation ($Sp_{O_2}$) (Nellcor, Hayward, CA, USA) and heart rate were monitored continuously and a respiration monitor (MR10, Graseby Medical, Watford, UK) constantly recorded ventilatory frequency. Respiratory depression was defined as ventilatory frequency $<8$ bpm and/or $Sp_{O_2}$ $<90\%$ and/or arterial $Pa_{CO_2}$ $>7.3$ kPa. Arterial blood-gas tensions were measured when $Sp_{O_2}$ $<90\%$ or $Pa_{CO_2}$ $>7.3$ kPa.

Postoperative alfentanil consumption and number of rewarded and unrewarded (during the lockout interval) demands were recorded. TCI was stopped if respiratory depression developed or if the patient wished to withdraw from the study. Side effects observed during the postoperative period were noted. The study was ended when the patient was discharged from the post-anaesthesia care unit. Patients had to stay in the post-anaesthesia care unit for at least 2 h. Postoperative analgesia after the study was prescribed by the responsible anaesthetist. For most patients, this was PCA morphine.

After operation arterial blood samples (3 ml) for measurement of plasma concentrations of alfentanil were obtained just before every change in target plasma concentration of alfentanil. A blood sample was also obtained 5 min after a new $C_T$ was achieved. The maximum amount of blood collected was restricted to 250 ml per patient. Plasma was obtained by centrifugation and stored at −20 °C until analysis. A capillary gas chromatographic technique[9] was used to determine plasma concentration of alfentanil. The detection limit was 0.1 ng $ml^{-1}$. The coefficient of variation in the concentration range ($>1$ ng $ml^{-1}$) in this study was $<5\%$.

A logistic regression model was fitted to the inadequate/adequate analgesia data *vs* measured plasma concentration of alfentanil obtained from the three groups. Adequate analgesia was defined as when the patient indicated no need for additional analgesia and had a VAS score $\leq 3.0$. Inadequate analgesia was defined as when the patient indicated a need for additional analgesia or had a VAS score $>3.0$. The logistic regression model is described by the following formula:

$$P=\frac{C_P{}^{\gamma}}{EC_{50}{}^{\gamma}+C_P{}^{\gamma}}$$

where $P$=probability of adequate analgesia, $C_P$=measured plasma concentration of alfentanil, $EC_{50}$=concentration corresponding to 50% probability that patients do not need additional analgesia and have a VAS score $\leq 3.0$ and $\gamma$=dimensionless variable indicating the sigmoidicity of the curve. $EC_{50}$ was considered to be 0 ng $ml^{-1}$ for patients that did not complain of pain during the study.

The predictive performance of the computer-controlled infusion system, implemented with the population pharmacokinetic data set from Maitre and colleagues,[7] was assessed by examining bias and inaccuracy, as described by Raemer and colleagues.[10] Bias is a measure of the systematic failure to achieve the target plasma concentration. Inaccuracy is a measure of the expected failure to achieve the target plasma concentration. Both bias and inaccuracy are aggregated measures of the performance of the system. For each blood sample the performance error (PE) was calculated as:

$$PE=\frac{(C_P-C_{pred})}{C_{pred}}\times 100$$

where $C_P$=measured plasma concentration of alfentanil and $C_{pred}$=corresponding predicted plasma concentration. The bias of the system is expressed as median PE (MDPE) for all blood samples. When 95% confidence intervals of the MDPE included zero, it was concluded that no significant bias had occurred. The system inaccuracy is the median of the absolute values of individual PE values (MDAPE). In addition, MDPE and MDAPE were also calculated for each patient from all blood samples collected from that patient. Data points with $C_T=0$ ng $ml^{-1}$ and $C_P<1$ ng $ml^{-1}$, where $C_T$ is the target plasma concentration of alfentanil, were omitted from this analysis.

For patients in the alfentanil group, the intraoperative alfentanil bolus doses were entered into a computer running a simulation program described by Hull[11] in order to calculate the concentrations of alfentanil in the three compartments at the start of postoperative analgesic therapy. Subsequently, cumulative volumes infused as stored by the computer were used to simulate new alfentanil concentrations as if the intraoperative alfentanil concentration had been taken into account by the computer. These new simulated alfentanil concentrations ($C_{sim}$) were then used to calculate the performance error of the blood samples of patients in the alfentanil group. For patients in the fentanyl and sufentanil groups, intraoperative opioid bolus doses were entered into the computer simulation program IVA-SIM (Schüttler, Kloos, Bonn, Germany) in order to predict the plasma concentration of fentanyl and sufentanil at the moment when the patient complained of pain.

Data were examined for normality using the Shapiro–Wilk test and are presented as mean (SD) or as median and 95% confidence interval (CI) or range, as appropriate. Patient data and variables describing the efficacy of treatment were compared using analysis of variance followed by the Newman–Keuls test, Kruskal–Wallis test or log-likelihood ratio test, as appropriate. Adverse reactions are reported as frequency of occurrence. For each patient, the number of observations with pain scores $>3.0$ were calculated. These numbers were then compared between the three groups using the Kruskal–Wallis test. $EC_{50}$ values were compared between groups using the Kruskal–Wallis test. $P<0.05$ was regarded as the minimum level of statistical significance.

## Results

We studied 37 patients; four patients in the fentanyl group and two in the sufentanil group did not report pain during the 2-h stay in the recovery room.

Data from one patient in the alfentanil group was excluded from analysis because of a surgical complication. Patient data, duration of anaesthesia, intraoperative opioid consumption and postoperative alfentanil consumption in the remaining 36 patients are presented in table 1 and did not differ between groups, except for intraoperative opioid consumption (not tested). No patient needed naloxone to restore adequate ventilation at the end of anaesthesia. All patients were breathing spontaneously on arrival in the post-anaesthesia care unit. As shown in

*Table 1* Patient characteristics, duration of anaesthesia, and intraoperative and postoperative opioid consumption (mean (SD))

| | Fentanyl ($n$=14) | Sufentanil ($n$=12) | Alfentanil ($n$=10) |
|---|---|---|---|
| Age (yr) | 37 | 43 | 42 |
| Weight (kg) | 73 (11) | 78 (16) | 70 (12) |
| Sex (M/F) | 7/7 | 5/7 | 3/7 |
| Duration of anaesthesia (min) | 166 (64) | 203 (63) | 147 (71) |
| Intraoperative opioid consumption (mg) | 0.6 (0.2) | 0.084 (0.036) | 13.2 (10.1) |
| Postoperative alfentanil consumption ($\mu g\ kg^{-1}\ min^{-1}$) | 0.28 (0.21) | 0.31 (0.21) | 0.37 (0.16) |

*Table 2* Onset of postoperative pain and satisfactory analgesia, end of loading period, total observation time and total number of demands (mean (SD) or median (range)). $^*P<0.05$ compared with fentanyl and sufentanil groups. (Patients who did not report pain during the study period are excluded)

| | Fentanyl ($n=10$) | Sufentanil ($n=10$) | Alfentanil ($n=10$) |
|---|---|---|---|
| Time from last intraoperative opioid injection to onset of postoperative pain (min) | 101 (52) | 136 (29) | 68 (19)* |
| Time from start therapy to onset of satisfactory analgesia (min) | 18 (5–40) | 15 (5–50) | 14 (5–50) |
| Time from start therapy to end loading period (min) | 72 (19) | 55 (22) | 56 (19) |
| Duration of observation (min) | 115 (7) | 114 (15) | 114 (12) |
| Total number of demands after loading | 6 (4–9) | 7 (2–14) | 7 (1–13) |

*Table 3* Number of observations awake with pain scores >3.0, awake with pain scores ≤3.0, asleep and total number of observations in the three groups All patients received a target-controlled infusion of alfentanil for postoperative pain relief. Values are median (range)

| | Fentanyl ($n=10$) | Sufentanil ($n=10$) | Alfentanil ($n=10$) |
|---|---|---|---|
| VAS >3.0 | 6 (3–9) | 7 (1–14) | 6.5 (1–13) |
| VAS ≤3.0 | 7.5 (1–21) | 6 (0–17) | 10 (6–16) |
| Asleep | 10.5 (0–15) | 10 (1–15) | 6 (0–13) |
| Total number of observations | 24 (22–25) | 24 (20–29) | 23 (19–27) |

table 2, postoperative pain treatment was started sooner ($P<0.05$) after the last intraoperative alfentanil bolus (mean 68 min), than after the last fentanyl (mean 101 min) or sufentanil bolus (mean 136 min). Measured concentrations of alfentanil for patients in group A at the moment they reported pain were 24–97 ng $ml^{-1}$ (median 56 ng $ml^{-1}$). The time after termination of anaesthesia when patients first reported pain did not differ between the three groups: 39 (20) min (group F), 41 (16) min (group S) and 41 (21) min (group A). All but three patients needed another increase in target concentration after the initial step of 20 ng $ml^{-1}$ to achieve adequate analgesia. There were no differences in duration of the loading period, total observation time (from the start of TCIA to the end of study) and total number of demands between the three groups (table 2). There were no unrewarded demands during the study. The number of observations where patients were asleep, awake with pain sores ≤3.0 and awake with pain scores >3.0 are shown in table 3 and did not differ between groups.

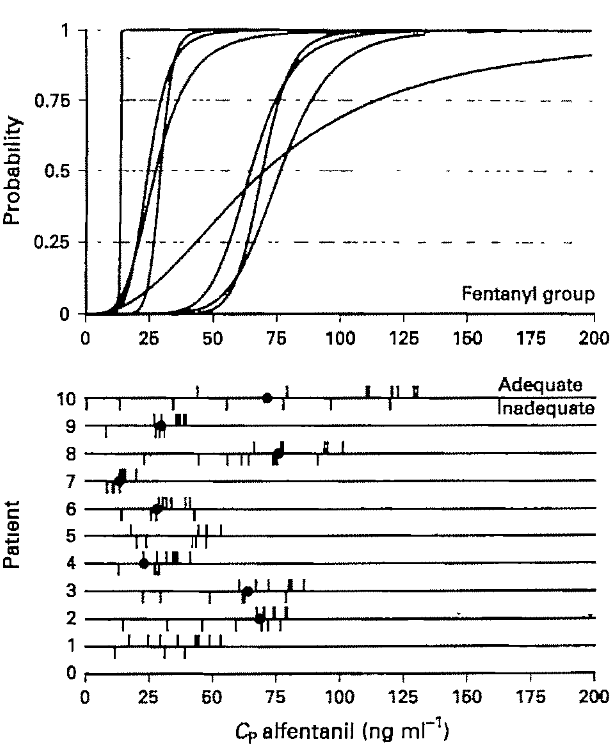

*Figure 1* Relationship between measured plasma concentration of alfentanil ($C_p$) and absence or presence of adequate analgesia in the postoperative period for individual patients in the fentanyl group. The lower panel represents the plasma concentrations of alfentanil and the associated presence or absence of adequate analgesia in patients in the fentanyl group. Adequate analgesia is indicated by an upward deflection, inadequate analgesia by a downward deflection. The $EC_{50}$ value is indicated by the large dot. For four patients who did not complain of pain during the study, $EC_{50}$ was considered to be 0 ng $ml^{-1}$.

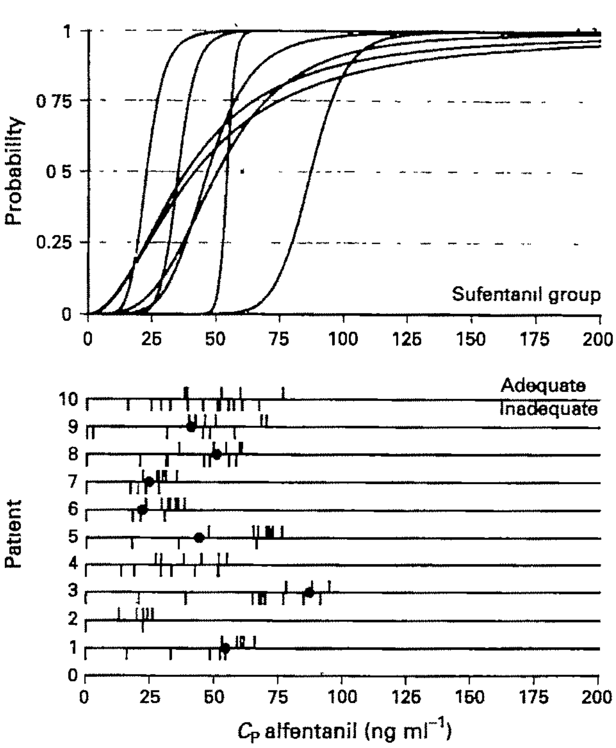

*Figure 2* Relationship between measured plasma concentration of alfentanil ($C_p$) and absence or presence of adequate analgesia in the postoperative period for individual patients in the sufentanil group. The lower panel represents the plasma concentrations of alfentanil and the associated presence or absence of adequate analgesia in patients in the sufentanil group. Adequate analgesia is indicated by an upward deflection, inadequate anelgesia by a downward deflection. The $EC_{50}$ value is indicated by the large dot For two patients who did not complain of pain during the study, $EC_{50}$ was considered to be 0 ng $ml^{-1}$.

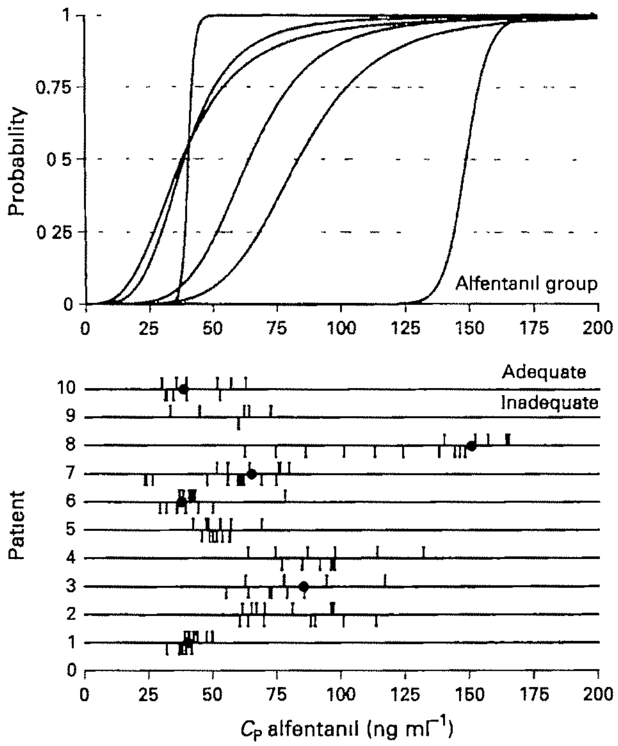

*Figure 3* Relationship between measured plasma concentration of alfentanil ($C_p$) and absence or presence of adequate analgesia in the postoperative period for individual patients in the alfentanil group. The lower panel represents the plasma concentrations of alfentanil and the associate presence or absence of adequate analgesia in patients in the alfentanil group. Adequate analgesia is indicated by an upward deflection, inadequate analgesia by a downward deflection The $EC_{50}$ value is indicated by the large dot.

The alfentanil concentration–effect relationships of individual patients in the three groups are shown in the figures 1–3. The $EC_{50}$ of alfentanil was median 26 ng ml$^{-1}$ (range 0–76 ng ml$^{-1}$) for group F, 39 (0-87) ng ml$^{-1}$ for group S and 52 (38–151) ng ml$^{-1}$ for group A. The $EC_{50}$ values of alfentanil, excluding patients that did not report pain, were 47 (13–76) ng ml$^{-1}$ for group F, 44 (23–87) ng ml$^{-1}$ for group S and 52 (38–151) ng ml$^{-1}$ for group A. The adequate/inadequate analgesia *vs* concentration data for individual patients are displayed underneath the curves. In one patient in group S (patient No. 2) and in one patient in group A (patient No. 9) there was only one observation with inadequate analgesia. The concentration–effect relationship of alfentanil therefore could not be determined in these patients. In two, one and three patients in groups F (patient Nos 1, 5), S (patient No. 10) and A (patient Nos 2, 4, 5), respectively, the model was unable to describe the data because there was too much overlap between adequate and inadequate analgesia. Inspection of the raw data suggested that the $EC_{50}$ of the patients in whom the concentration–effect relationship could not be determined was likely to be in the same range as those of the other patients.

The bias and inaccuracy of the system calculated from all blood samples were, respectively, −1 (95% CI −7 to +7) % and 20 (15–22) % in the fentanyl group, −6 (−14 to 0) % and 21 (18–26) % in the sufentanil group and −2 (−8 to +10) % and 33 (25–37) % in the alfentanil group for the simulated predicted values. As the confidence limits included zero, there was no significant bias.

Ventilatory frequency and postoperative $Sp_{O_2}$ were always within the clinically acceptable range. Sedation score was ≤3 in all patients at all times. No patient developed hypotension, defined as a decrease in arterial pressure of more than 15% from preoperative control values. Four patients in group F, three in group S and three in group A needed an antiemetic for nausea or vomiting. In one patient in group F itching occurred.

## Discussion

The main objective of this study was to evaluate the efficacy of target-controlled infusion of alfentanil during the initial recovery period and at the same time to investigate the pharmacodynamics of alfentanil in individual patients. This study was designed such that the concentration–effect relationship was determined after administration of balanced anaesthesia, as used in clinical practice. The onset of the analgesic effect in the postoperative period depends on the characteristics (distribution, elimination and rapidity of its equilibration between blood and brain) of the drug administered in the postoperative period. Analgesic drugs used in the operating theatre may also affect the patient in the postoperative period. In this study intraoperative anaesthesia was provided by enflurane or isoflurane and nitrous oxide supplemented with fentanyl, sufentanil or alfentanil. As expected, we found that patients experienced postoperative pain significantly faster after the last intraoperative bolus of alfentanil than after fentanyl and sufentanil. However, the three groups did not differ in the time interval from the end of anaesthesia to onset of postoperative pain.

In studies where i.v. infusion regimens of alfentanil have been used for analgesia in the postoperative period, inadequate analgesia and respiratory problems have occurred directly after the start of the regimen.[12 13] To date, limited data are available on the use of TCIA only in the postoperative period. The aim of postoperative pain management is to relieve the patient's pain and to increase comfort. In our opinion the best analgesic regimen results in minimization of painful periods without side effects. To test the TCI regimen in the postoperative phase we therefore chose an initial step of 20 ng ml$^{-1}$ when patients first complained of pain. All but three patients (one from each group) needed another increase in target concentration after the initial step to achieve adequate analgesia. It is possible that in the three patients who did not need a further increase in target concentration, adequate analgesia might have been reached with a target concentration<20 ng ml$^{-1}$. However, none of these three patients had any adverse effects, in particular no respiratory depression. We feel therefore that an initial target concentration of 20 ng ml$^{-1}$ is satisfactory. In a previous study we reported a minimum effective analgesic concentration (MEAC) of alfentanil in the immediate postoperative period of 59 ng ml$^{-1}$.[6] With the regimen used in this study, 60 ng ml$^{-1}$ could be

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achieved in 25 min. In this study we did not encounter respiratory depression with a step size of 10 ng ml$^{-1}$ and a lockout time of 5 min during the loading period, irrespective of the intraoperative opioid used.

To study the pharmacodynamics of alfentanil, we defined a quantal effect parameter, which considered pain relief as either adequate or inadequate. The criteria for adequate analgesia were: (1) quality of analgesia, which was adequate when the patient indicated no need for additional analgesia or was asleep and (2) VAS score $\leqslant$3.0. Inadequate analgesia was defined as: (1) activation of the TCI system or (2) VAS scores $>$3.0. We chose a cut-off value of the pain score of 3.0 as patients in a previous study using TCI alfentanil were generally satisfied with the therapy at this score.[1]

Our results showed a variability in individual values of EC$_{50}$ ranging from 0 to 151 ng ml$^{-1}$. These results are in agreement with a study where we reported a median minimum effective analgesic concentration of alfentanil of 59 ng ml$^{-1}$ (range 26–159 ng ml$^{-1}$) at the start of therapy for a group of 20 orthopaedic patients.[6] The wide inter-individual variability is well known from the literature and not surprising considering the different types of surgery and the fact that residual concentrations of drugs used during operation, including volatile anaesthetics, were still present during the study. The EC$_{50}$ values did not differ between the groups. As residual concentrations of opioids administered during operation were present during the study, we anticipated that EC$_{50}$ values in patients who had received fentanyl or sufentanil would have been lower than in patients who had received alfentanil during operation. The simulated plasma concentrations of the three drugs administered during operation at the moment when patients reported pain were, on average, 1.7 ng ml$^{-1}$ (range 0.8–3.0 ng ml$^{-1}$) for the fentanyl group, 0.10 (0.04–0.16) ng ml$^{-1}$ for the sufentanil group and 44 (18–141) ng ml$^{-1}$ for the alfentanil group. These concentrations are similar to the reported MEAC values after i.v. administration of different drugs.[6 14–16] During the 2-h study, plasma concentrations of the three drugs administered during operation decreased. At the end of the loading period the simulated plasma concentration of fentanyl had decreased to 1.2 ng ml$^{-1}$ and that of sufentanil to 0.08 ng ml$^{-1}$. The simulated plasma concentrations for patients that did not report pain during the study were in the same range as the plasma concentrations of the patients that used TCIA. EC$_{50}$ values reported in this study were comparable to MEAC values reported in a study[6] where the patient population was strictly standardized. As the EC$_{50}$ of alfentanil did not differ between the three groups, we could not demonstrate differences in postoperative pharmacodynamics of alfentanil between patients that had received balanced analgesia with different opioids. This does not exclude the fact that opioids administered during operation contribute to postoperative analgesia. However, to quantify the contribution of intraoperative opioids on postoperative analgesia would require much larger patient groups.

The performance error was calculated in order to investigate the applicability of a population pharmacokinetic data set in a TCIA after operation. The population pharmacokinetic data described by Maitre and colleagues[7] were obtained from intraoperative studies and therefore might not be optimal for the postoperative period. As the 95% confidence interval for the MDPE included 0 for all three groups, there was no bias. The inaccuracy resulting from implementation of the population pharmacokinetic data set resulted in acceptable MDAPE values of 20–33%. Therefore, the population pharmacokinetic data set described by Maitre and colleagues[7] can be used in a postoperative TCIA regimen.

In summary, TCIA as a postoperative analgesic technique under the conditions studied (initial target concentration of 20 ng ml$^{-1}$, step size of 5–10 ng ml$^{-1}$ with a lockout time of 5 min) was an acceptable technique with a fast onset of satisfactory analgesia. Irrespective of the opioid administered during operation, inter-individual variability in the postoperative pharmacodynamics of alfentanil was large. However, the TCIA regimen easily overcomes this variability so that all patients are rapidly titrated to adequate analgesia.

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# I.v. perioperative ketoprofen in small children during adenoidectomy

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## Summary

We have investigated the analgesic and opioid sparing effect of perioperative i.v. ketoprofen in a randomized, double-blind, placebo-controlled, parallel group study in 164 children, aged 1–7 yr, after adenoidectomy. A standard anaesthetic method was used and all children received fentanyl 1 $\mu g\ kg^{-1}$ i.v. during induction. Children in the ketoprofen group received ketoprofen 1 mg $kg^{-1}$ i.v. after induction of anaesthesia followed by an infusion of ketoprofen 1 mg $kg^{-1}$ over 2 h. Children in the placebo group received 0.9% saline. All children received fentanyl 1 $\mu g\ kg^{-1}$ i.v. as rescue analgesia. In the ketoprofen group less children required postoperative fentanyl (64% *vs* 77%, $P=0.006$) and the total number of fentanyl doses was smaller compared with the placebo group (mean 1.0 (SD 1.1) (95% confidence intervals (CI) 0.8–1.3) *vs* 1.5 (1.1) (95% CI 1.2–1.7), $P=0.012$). Worst pain observed in the postanaesthesia care unit was also lower in the ketoprofen group both at rest ($P=0.028$) and during swallowing ($P=0.001$). There were no difference in the number of adverse reactions between the groups. No serious adverse reactions occurred. (*Br. J. Anaesth.* 1997; **78**: 24–27)

**Key words**
Anaesthesia, paediatric. Pain, postoperative. Analgesics non-opioid, ketoprofen. Analgesia, pre-emptive. Surgery, otolaryngological. Children.

Adenoidectomy is one of the most common surgical procedures in childhood. Frequently it is carried out as a day-case operation and children should be painless and alert when leaving hospital. Opioids provide effective analgesia, but also have known side effects such as emesis, sedation and risk of respiratory depression. This restricts the use of opioids after operation during day-case surgery.

The use of non-steroidal anti-inflammatory drugs (NSAID) has been shown to reduce the need for opioids after operation in children.[1] Ketoprofen is a NSAID with a chemical composition of 2-(3-benzophenyl)-propionic acid.[2] It is available in i.v., i.m., oral and rectal formulations. I.v. administration is the most accurate and the most practical route during general anaesthesia. Ketoprofen has proved to provide good postoperative analgesia in adults.[3] In children, it has been studied as an antipyretic agent.[4]

The aim of this study was to investigate the analgesic and opioid sparing effect of i.v. ketoprofen in children aged 1–7 yr after adenoidectomy.

## Patients and methods

The study was approved by the Ethics Committee of Kuopio University Hospital and the parents of patients gave written informed consent.

We studied 164 patients, ASA I or II, aged 1–7 years, undergoing adenoidectomy (with or without myringotomy, tympanostomy or sinus lavage). Patients were excluded if they had a known allergy to ketoprofen or other non-steroidal anti-inflammatory medication, asthma, kidney or liver dysfunction or haemorrhagic diathesis.

A randomized, double-blind, placebo-controlled, parallel group study design was used. Children were allocated randomly to either the ketoprofen or placebo group. After induction of anaesthesia, children in the ketoprofen group received ketoprofen 1 mg $kg^{-1}$ (Orudis, Rhone- Poulenc-Rorer, Denmark) dissolved in 10 ml of 0.9% saline injected over 10 min i.v. as a loading dose followed by an infusion of ketoprofen 1 mg $kg^{-1}$ dissolved in 40 ml of 0.9% saline over 2 h. The total dose of ketoprofen in the ketoprofen group was 2 mg $kg^{-1}$. Children in the placebo group received 0.9% saline for the loading dose and infusion. All children received fentanyl 50 $\mu g\ ml^{-1}$ i.v. as rescue analgesia if required.

A standard anaesthetic technique was used in all children. Each child was premedicated with diazapam 0.5 mg $kg^{-1}$ orally up to a maximum of 10 mg, 30–45 min before induction of anaesthesia. EMLA cream (Astra, Sweden) was used for venous puncture sites.

Anaesthesia was induced with thiopentone 5–7 mg $kg^{-1}$ and fentanyl 1 $\mu g\ kg^{-1}$ i.v. and tracheal intubation was facilitated with atracurium 0.5 mg $kg^{-1}$. Anaesthesia was maintained with 1–1.2% isoflurane (inspired concentration) and 65% nitrous oxide in oxygen with IPPV. On completion of the procedure neuromuscular block was antagonized with neostigmine 50 $\mu g\ kg^{-1}$ and glycopyrronium 10 $\mu g\ kg^{-1}$. All children received fentanyl 1 $\mu g\ kg^{-1}$ i.v. at induction and no more opioid was allowed during operation.

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All children were given 0.9% saline 10 ml kg$^{-1}$ h$^{-1}$ for intraoperative maintenance. The children were transferred to the post-anaesthesia care unit (PACU) for continuous monitoring of vital signs and assessment of pain.

Postoperative pain was assessed by the Maunuksela score.[5] The Maunuksela score is an observer assessment based on mimic, vocalization, movement or rigidity of the limbs and body, response to handling and irritability, together with measured cardiorespiratory variables. In the modified score 0="no pain", 1–3="slight pain", 4–6="moderate pain", 7–9="severe pain" and 10="worst possible pain".

Specially trained research nurses assessed the pain experienced by the child at rest and during swallowing. If the child was in pain (pain score at rest was 3 or more) fentanyl 1 μg kg$^{-1}$ was given i.v. for rescue analgesia. The dose was repeated in 5-min intervals until the child was comfortable. No more than three doses of fentanyl were allowed in 1 h. No other analgesic medication was permitted during the study. The children were monitored closely after each dose of fentanyl in the PACU.

When leaving hospital, pain was assessed by nurses using a 100-mm long visual analogue scale (VAS) (0="no pain" and 100="worst possible pain") at rest and during swallowing.[6] Sedation was assessed at the same time using the 100-mm VAS: 0="full alert" and 100="not arousable". All adverse reactions were recorded and summarized for each patient.

The adenoids were removed using indirect curettization. Haemostasis was controlled with nasopharyngeal packs with or without electrocautery. Surgeons estimated the amount of bleeding using a five-point scale: 1=no bleeding, 2=less than normal, 3=normal, 4=more than normal, 5=profuse.

Based on the results of our earlier study[1] a power calculation determined that a sample size of 79 children per group would be required to demonstrate a 30% reduction in the need for opioids. This gave the study 80% power at a significance level of 0.05. Analysis of variables was performed using the two-tailed Student's *t* test, chi-square test and binominal test. $P<0.05$ was considered statistically significant. Results are presented as mean (SD) (95% confidence interval (CI) or range) where appropriate.

## Results

There were no differences between the two groups in sex distribution, age, weight, height or ASA status (table 1) or in the type of surgery performed (table 2).

I.v ketoprofen 1 mg kg$^{-1}$ bolus during anaesthesia followed by an infusion of 1 mg kg$^{-1}$ over 2 h reduced the number of children requiring supplementary doses of fentanyl. In the ketoprofen group, 51 (64%) children and in the placebo group 65 (77%) children received fentanyl ($P=0.006$). Children in the ketoprofen group received fewer fentanyl doses (1.0 (1.1) (95% CI 0.8–1.3)) than children in the placebo group (1.5 (1.1) 95% CI (1.2–1.7), $P=0.012$) (table 3). The number of children who received either none or only one dose of fentanyl was significantly greater in the ketoprofen (60 (75%)) than in the placebo (44 (52%)) group ($P=0.003$). Those children in the ketoprofen group who received fentanyl as rescue analgesia required slightly fewer fentanyl doses than children in the placebo group, but this was not significant ($P=0.104$). In those children who received fentanyl as rescue analgesia the number of children who received only one dose of fentanyl was significantly less in the ketoprofen group (31 (61%)) than in the placebo group (25 (38%), $P=0.017$) (table 4).

*Table 1* Patient data for the two groups (mean (SD) and [range])

| | Ketoprofen ($n$ = 80) | Placebo ($n$ = 84) |
|---|---|---|
| Sex (M/F) | 52/28 | 44/40 |
| Weight (kg) | 16 (5) [10–32] | 16 (5) [9–31] |
| Height (cm) | 97 (16) [75–140] | 97 (16) [75–135] |
| Age (months) | 38 [12–111] | 40 [10–95] |
| ASA (I/II) | 77/3 | 79/5 |

*Table 2* Type of surgery in the two groups (number)

| | Ketoprofen ($n$=80) | Placebo ($n$=84) |
|---|---|---|
| Adenoidectomy | 46 | 35 |
| Adenoidectomy and myringotomy | 7 | 10 |
| Adenoidectomy and tympanostomy | 13 | 25 |
| Adenoidectomy and sinus lavage | 7 | 7 |
| Adenoidectomy and tympanostomy and sinus lavage | 3 | 2 |
| Adenoidectomy and other combination | 4 | 5 |

There were no differences in Maunuksela pain scores 1 h after operation in the PACU (table 5). Two hours after surgery pain scores during swallowing in the ketoprofen group (0.8 (1.7)) were lower compared with the placebo group (2.0 (2.6), $P=0.006$). At rest the difference between the groups was not significant ($P=0.065$). Worst pain observed

*Table 3* Number of fentanyl doses in the post-anaesthesia care unit during the first 2 h ($n$ (%), mean (SD), range and 95% confidence intervals (CI). *$P<0.05$ ($t$ test); **$P<0.01$ (chi-square test)

| | | Ketoprofen ($n$=80) | Placebo ($n$=84) |
|---|---|---|---|
| No of fentanyl doses | | | |
| $n$ (%) | ≤1 | 60 (75) | 44 (52)** |
| | >1 | 20 (25) | 40 (48) |
| Mean (SD) | | 1.0 (1.1) | 1.5 (1.1)* |
| Range | | 0–5 | 0–6 |
| 95% CI | | 0.8–1.3 | 1.2–1.7 |

*Table 4* Number of fentanyl doses during the first 2 h in those children who required fentanyl treatment in the post-anaesthesia care unit ($n$ (%), mean(SD) and 95% confidence intervals (CI)). *$P<0.05$ (chi-square test)

| | | Ketoprofen ($n$ = 51) | Placebo ($n$ = 65) |
|---|---|---|---|
| No of fentanyl doses | | | |
| $n$ (%) | 1 | 31 (61) | 25 (38)* |
| | >1 | 20 (39) | 40 (62) |
| Mean (SD) | | 1.6 (0.9) | 1.9 (0.9) |
| 95% CI | | 1.3–1.9 | 1.7–2.1 |

*Table 5* Maunuksela pain scores in the post-anaesthesia care unit (PACU) (mean (SD) [range])

| | Ketoprofen | Placebo | *P*, *t* test |
|---|---|---|---|
| After 1 h | | | |
| At rest | 1.2 (2.4) [0–9] | 0.9 (2.1) [0–9] | 0.437 |
| Swallowing | 2.8 (2.9) [0–9] | 2.8 (3.4) [0–10] | 0.923 |
| After 2 h | | | |
| At rest | 0.4 (1.5) [0–9] | 0.9 (2.0) [0–9] | 0.065 |
| Swallowing | 0.8 (1.7) [0–7] | 2.0 (2.6) [0–9] | 0.006 |
| At leaving the PACU | | | |
| At rest | 0.2 (0.5) [0–3] | 0.3 (1.0) [0–5] | 0.399 |
| Swallowing | 0.4 (0.8) [0–3] | 0.6 (1.3) [0–8] | 0.432 |
| Worst pain in the PACU | | | |
| At rest | 1.9 (2.4) [0–9] | 2.9 (2.7) [0–9] | 0.028 |
| Swallowing | 2.9 (2.7) [0–9] | 4.5 (2.9) [0–10] | 0.001 |

*Table 6* Number of adverse reactions in the post-anaesthesia care unit (*n* (%)). **P*<0.05 (binominal test)

| | Ketoprofen (*n* = 80) | Placebo (*n* = 84) |
|---|---|---|
| Nausea and/or vomiting | 13 (16) | 7 (8)* |
| Epigastric distress | 1 (1) | 1 (1) |
| Other abdominal pain | 3 (4) | – |
| Somnolence | 6 (7) | 15 (19)* |
| Urination problems (delayed or difficult) | 4 (5) | 4 (5) |
| Pain or redness in the puncture site | 1 (1) | 1 (1) |
| Mild neurological symptoms (cephalalgia, vertigo, visual disturbance) | 2 (2) | 1 (1) |
| Other (shivering, irritability, breath weakness) | 4 (5) | – |
| Total No. of adverse reactions | 34 | 30 |
| No. of children with adverse reactions | 20 (25) | 23 (27) |
| Mean (SD) | 0.4 (0.9) | 0.4 (0.7) |

in the PACU was lower in the ketoprofen group compared with the placebo group both at rest ($P$=0.028) and during swallowing ($P$=0.001).

When discharged there was no difference in pain scores between the groups. Children in the ketoprofen group were slightly less sedated than children in the placebo group, but this was not significant ($P$=0.099).

In the PACU there was no difference in the frequency of adverse reactions between the groups (table 6). In the ketoprofen group 20 children (25%) and in the placebo group 23 children (27%) had one or more adverse reactions. In the ketoprofen group children had more nausea and vomiting than in the placebo group ($P$=0.018). Somnolence was more frequent in the placebo group than in the ketoprofen group ($P$=0.013). There were no serious adverse reactions and the medication was discontinued in only one patient in the ketoprofen group because of gastrointestinal discomfort during infusion.

The time between operation and first urination was significantly shorter in the ketoprofen group (160 (46) min) than in the placebo group (191 (49) min, $P$=0.001).

There were no significant differences in pain scores if only adenoidectomy or adenoidectomy and one or more of the additional operations were considered.

To assess if the age of the children had any effect on pain scores or the need for rescue analgesia, we divided the groups into three age groups: 24 months or less; 25–48 months and over 48 months. There were no differences between the age groups.

*Table 7* Intraoperative bleeding estimated by the surgeon (*n* (%)). *P*<0.05 (chi-square test) between groups

| | Ketoprofen (*n* = 80) | Placebo (*n* = 84) |
|---|---|---|
| Less than normal | 6 (7) | 9 (11) |
| Normal | 62 (78) | 72 (85) |
| More than normal | 12 (15) | 3 (4) |

The surgeon estimated the amount of intraoperative bleeding using a five-point scale. Twelve (15%) children in the ketoprofen group and three (4%) children in the placebo group were classified as bleeding “more than normal”. Six (7%) children in the ketoprofen group and nine (11%) in the placebo group were classified as bleeding “less than normal”. The difference between the groups was significant ($P$=0.037) (table 7). There were no children in either group who experienced postoperative bleeding which would have required intervention or return to the operating theatre or which would have caused any delay on discharge from hospital.

## Discussion

In this study we showed that intraoperative ketoprofen i.v. followed by constant infusion over 2 h significantly reduced (30% reduction) the need for fentanyl after operation in small children after adenoidectomy. Patients in the ketoprofen group needed significantly less fentanyl doses in the PACU than patients in the placebo group. Also, the number of the children who required fentanyl treatment was significantly smaller in the ketoprofen group than in the placebo group. Further, those children who required fentanyl in the ketoprofen group seemed to require slightly fewer doses than those children in the placebo group. Although this finding was not statistically significant, a tendency was clear. Our data suggest that intraoperative administration of ketoprofen to children reinforces opioid-induced analgesia without increased risk of serious adverse reactions.

Two hours after operation children in the ketoprofen group had significantly less pain than children in the placebo group during swallowing. At rest the ketoprofen group also had less pain, but the difference was not significant. This tendency was not seen 1 h after operation. These results indicate a relatively slow onset of the analgesic effect of i.v. ketoprofen. This has been shown also with other analgesics which act via inhibition of prostaglandin synthesis.[7]

The incidence of adverse reactions in previous studies varied widely from none of significance to approximately 50% of patients.[2] In our study, incidences were 25% in the ketoprofen group and 27% in the placebo group. In the placebo group children experienced somnolence significantly more often after operation than children in the ketoprofen group ($P$=0.013). This can be explained by the more frequent doses of fentanyl in the placebo group compared with the ketoprofen group. In the ketoprofen group children had more nausea and vomiting than children in the placebo group ($P$=0.018). In previous studies the increased frequency of postoperative nausea was associated with concomitant use of NSAID and opioid.[8] There were no serious adverse reactions in this study and in only one patient was the medication discontinued. This patient was a 7-yr-old boy in the ketoprofen group and he experienced gastrointestinal discomfort. His symptoms were alleviated immediately after the medication was discontinued. The incidence and scale of adverse reactions in this study were comparable with other studies with short-term use of NSAID in children.[1, 7]

Transient depression of renal function is a known effect of NSAID.[9, 10] The risk of renal failure is highest in patients with diminished renal perfusion caused by hypovolaemia or hypotension, for example. In this study all children received an infusion of 0.9% saline in the perioperative period. No signs of depression of renal function were seen. The time between operation and first urination was significantly longer in the placebo group than in the ketoprofen group, probably because of the greater degree of sedation in the placebo group caused by the greater doses of fentanyl.

Splinter and colleagues showed that preoperative use of ketorolac 1 mg kg$^{-1}$ increased perioperative bleeding in children with tonsillectomy.[11] We found that a ketorolac dose of 1 mg kg$^{-1}$ was rather high. In previous studies, a dose of 0.5 mg kg$^{-1}$ and even a dose of 0.2 mg kg$^{-1}$ had a good analgesic effect after major surgery in children.[7] In our study perioperative bleeding was estimated by the surgeon and was greater in the ketoprofen group than in the placebo group. In all children haemostasis was maintained with nasopharyngeal packs with or without electrocautery. None of the children experienced post-operative bleeding which required intervention or delay in discharge from hospital.

In day-case surgery in children it is important that parents feel safe to leave the hospital with their child. Therefore, a child should be as painless and as alert as possible. In this study children had minimal pain and low sedation scores when discharged. However, there was a tendency for children in the ketoprofen group to be even more alert and have less pain than children in the placebo group.

In this study we used ketoprofen 1 mg kg$^{-1}$ during general anaesthesia and an infusion of 1 mg kg$^{-1}$ after operation for 2 h. Ketoprofen has been shown to have a good antipyretic effect at an oral dose of 0.5 mg kg$^{-1}$ but the effect was significantly better with a dose of 1 mg kg$^{-1}$.[4] Further investigations are needed to find an optimal i.v. ketoprofen dose for children in the treatment of postoperative pain.

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# Effect of clonidine on gastric emptying of liquids

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**Summary**

We have investigated the effects of clonidine on gastric emptying of liquids in 30 patients. In a double-blind, randomized design, clonidine 150 μg, morphine 10 mg or saline in 1 ml was given i.m. One hour later, the patient drank a paracetamol solution (1.5 g in 50 ml water). Venous blood samples were obtained every 15 min for 90 min thereafter. Plasma paracetamol concentrations were measured using high-pressure liquid chromatography and the area under the concentration–time curve was calculated. The degree of sedation and complications were recorded. The area under the curve for 0–60 min was significantly smaller in the morphine group than in the saline group ($P$=0.002; 95% confidence interval (CI) for difference −1237 to −502 μg min ml$^{-1}$), whereas it was greater in the clonidine group compared with the saline group, although this was not significant (95% CI for difference −423 to 1264 μg min ml$^{-1}$). Arterial pressure was significantly lower in the clonidine group compared with the saline group. Both clonidine and morphine appeared to cause mild sedation. We conclude that clonidine 150 μg i.m. does not delay gastric emptying of liquids in a similar manner to morphine. (*Br. J. Anaesth.* 1997; **78**: 28–33)

**Key words**

Gastrointestinal tract, emptying. Sympathetic nervous system, clonidine. Pharmacology, clonidine.

Delay in gastric emptying may induce nausea and vomiting which may increase the risk of pulmonary aspiration of gastric contents during the perioperative period. It may also delay absorption of orally administered drugs. In critically ill patients whose lungs are ventilated mechanically, delay in gastric emptying causes bacterial overgrowth in the gastrointestinal tract and increases the incidence of pulmonary infection.[1] Opioids, which have been used widely for premedication, markedly delay the rate of gastric emptying.[2–4]

Alpha$_2$ adrenoceptor agonists, such as clonidine, reduce anxiety, induce sedation and possibly produce analgesia.[5 6] They decrease the requirements for opioid and inhalation agents during induction and maintenance of anaesthesia and provide haemodynamic stability.[5 6] Alpha$_2$ agonists also produce less respiratory depression, nausea and vomiting, or pruritus than opioids.[5 6] Thus the use of $\alpha_2$ adrenoceptor agonists as adjunctive agents has received considerable attention.

The effects of $\alpha_2$ agonists on gastric emptying have been studied, but the results are inconclusive.[7–11] In some studies in rodents, $\alpha_2$ adrenoceptor agonists injected subcutaneously did not delay gastric emptying of liquids,[7–9] whereas in other studies the agonists delayed emptying.[10 11] In humans, oral clonidine did not significantly delay gastric emptying of radiolabelled solid food,[12] whereas lidamidine, which is also considered as an $\alpha_2$ adrenoceptor agonist, delayed gastric emptying of solid food.[13]

The rate and mechanism of gastric emptying differ considerably for liquids and digestible solids.[14 15] The effect of $\alpha_2$ adrenoceptor agonists on gastric emptying of liquids in humans has not been studied. The main aim of this study therefore was to examine the effect of clonidine on gastric emptying of liquids in humans.

## Patients and methods

In a double-blind, randomized design, before induction of anaesthesia, we studied 30 patients (ASA I or II) undergoing routine gynaecological surgery. Patients with a history of gastrointestinal, heart, hepatic and renal disease were excluded. Patients in whom systolic arterial pressure was either greater than 160 mm Hg or less than 100 mm Hg, or had a heart rate less than 60 beat min$^{-1}$, and those receiving any other medications or with a history of allergic reaction to any drug were excluded. The local research Ethics Committee approved the study and written informed consent was obtained from all patients.

Patients were asked not to eat solid food for at least 5 h and not to drink liquids for 2 h before the start of the study. No premedication was given. Approximately 3 h before induction of anaesthesia,

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the patient was transferred to a quiet area in the recovery room. An electrocardiograph and non-invasive arterial pressure monitor were attached to the patient. A large-gauge i.v. cannula was inserted under local anaesthesia into the antecubital fossa for blood sampling. Patients were asked to stay in a semi-recumbent position throughout the study.[16] They were also asked to refrain from drinking, eating and smoking.

Patients were allocated randomly to one of three groups. Block randomization (in blocks of 12) was used for allocation and cards indicating allocations were placed in serially numbered, sealed opaque envelops: clonidine group, clonidine 150 μg in a volume of 1 ml; morphine group, morphine 10 mg in a volume of 1 ml; saline group, saline 1 ml.

One anaesthetist prepared the study drug shortly before the start of the study. The second anaesthetist injected the test drug into the anterolateral aspect of the thigh muscle. Both the second anaesthetist and patients were unaware of the randomization.

Gastric emptying was assessed by measuring the plasma concentrations of paracetamol after oral ingestion.[17 18] One hour after injection of the test drug, 50 ml of water containing paracetamol 1.5 g were given orally. We decided that the time from injection of the test drug to ingestion of paracetamol solution should be 1 h, because both the plasma concentration and analgesic effect of i.m. clonidine are maximal at about 1 h.[19] Venous blood (10 ml) was obtained every 15 min for 90 min after ingestion. Each blood sample was placed immediately in an individual tube containing heparin. Plasma was obtained using a centrifuge (CS-15R Centrifuge, Beckman) with a speed of 3000 $\text{min}^{-1}$ for 10 min; temperature in the centrifuge was set as 4 °C. Plasma was stored at $-20$ °C until paracetamol concentrations were measured.

Plasma paracetamol concentration was measured using high-pressure liquid chromatography.[20] The sensitivity of the chromatographic method was 0.1 $\mu g\ ml^{-1}$ of plasma paracetamol. The intra-assay coefficient of variation, that is the precision of the assay for quality control samples prepared at 5, 10 and 50 $\mu g\ ml^{-1}$, was less than 3%. The inter-assay coefficient of variation, that is the accuracy of the assay for the same quality control samples, was less than 5%.

The degree of sedation was examined before, and at 1 and 2.5 h after administration of the test drug. The degree of sedation was scored as follows: 1=awake, 2=drowsy or sleeping, easy to arouse by verbal contact, 3=asleep, difficult to arouse, 4=asleep, not arousable. Any incidence of vomiting, pruritus or dryness of mouth was also recorded.

Arterial pressure and heart rate were monitored throughout. If systolic arterial pressure decreased by more than 30% of the pre-injection value, crystalloid fluid in a volume up to 500 ml was given. Fluid was infused through another i.v. cannula which was inserted into the other arm to avoid possible dilution of the blood sample for paracetamol assay. If arterial pressure was still low, incremental doses of ephedrine 3 mg i.v. were given. If heart rate decreased to less than 45 beat $\text{min}^{-1}$, atropine 0.6 mg was given. If either ephedrine or atropine, or both, were given, patients were withdrawn from the study.

### STATISTICAL ANALYSIS

Median maximum plasma paracetamol concentration ($C_P$max), time to maximum concentration ($tC_P$max), area under the concentration–time curve (AUC) and 95% confidence interval (CI) for each value were calculated. The area was calculated based on the trapezoidal rule.[21]

Hypothesis tests were used only for AUC. Normal plots (plots of normal scores) and Shapiro–Francia $W'$ test[21] showed that the data were normally distributed; however, the $F$ test showed that the variability between the three groups was significantly different. Therefore, the Kruskal–Wallis test was used to compare AUC values between groups. If this proved significant, the Mann–Whitney $U$ test was used to compare AUC between the clonidine and saline groups, and between the morphine and saline groups. $P$ values were adjusted for ties. $P<0.05$ was considered significant.

Differences between two groups in AUC, $C_P$max and $tC_P$max were described by medians and 95% confidence intervals (CI). CI values for medians were calculated using the Sinterval command (sign test) in Minitab Release 8.2, which shows a confidence level close to 95%.

Mean arterial pressure and heart rate at 1 and 2.5 h after administration of the test drug were expressed as difference from pre-injection values. The maximum difference was also obtained. The 95% CI for differences between two groups were calculated.

There is no apparent criterion to decide the clinically relevant difference in AUC between the control and test groups. In one study, in which the same dose of paracetamol in the same volume of water was used as in this study (1.5 g in 50 ml), morphine 10 mg i.m. decreased $\text{AUC}_{0\text{-}90\ \text{min}}$ by 59%.[4] We considered that a reduction in AUC by a test drug of 50% would be a clinically relevant difference. To detect this reduction, with a power of 0.9 and $P=0.05$, approximately eight patients in each group were required.[21 22] We considered that smaller changes in AUC could be assessed using 95% CI. Therefore, we decided to study 30 patients, expecting withdrawal of a few patients from the test groups because of possible complications.

## Results

Ten patients were allocated to the saline group, 11 to the morphine group and nine to the clonidine group. One patient, in whom morphine had been given, vomited shortly after ingestion of the paracetamol solution. Data from this patient were not used for analysis. In two patients in the clonidine group, it was not possible to obtain the blood sample at 90 min because the patient was transferred to the anaesthetic room. Age, weight and height of the patients were similar in the three groups (table 1).

Morphine 10 mg i.m. significantly delayed gastric emptying, whereas clonidine 150 μg i.m. did not

*Table 1* Patient characteristics (mean (SD) [range])

| | Saline group ($n$=10) | Clonidine group ($n$=9) | Morphine group ($n$=11) |
|---|---|---|---|
| Age (yr) | 40 [25–46] | 42 [21–66] | 40 [22–66] |
| Weight (kg) | 66 (13.5)[52–90] | 65 (13.4) [51–85] | 73 (10.9) [55–90] |
| Height (cm) | 161 (3.9) [155–168] | 158 (5.0) [150–168] | 162 (6.0) [147–170] |

*Table 2* Area under the concentration–time curve for 0–60 min after ingestion of the paracetamol solution ($AUC_{0-60min}$), maximum plasma paracetamol concentration ($C_p$max) and time to maximum concentration ($tC_p$max) for each group and the differences between groups (median (95% confidence limits)) Paracetamol was given 60 min after i.m. injection of the test drug (saline, clonidine 150 μg or morphine 10 mg in 1 ml). Hypothesis tests were used only for $AUC_{0-60min}$. Non-parametric one-way analysis of variance (Kruskal–Wallis test) showed a significant difference in $AUC_{0-60min}$ between groups ($P<0.001$); the Mann–Whitney $U$ test was used to compare morphine and saline groups and clonidine and saline groups

| | $AUC_{0-60min}$ (μg min ml$^{-1}$) | $P$ | $C_p$max (μg ml$^{-1}$) | $tC_p$max (min) |
|---|---|---|---|---|
| Saline group ($n$=10) | 1371 [873, 1695] | — | 30.0 [24.2, 38.0] | 15.0 [15.0, 50.1] |
| Clonidine group ($n$=9) | 1840 [914, 2718] | — | 35.7 [22.3, 57.4] | 30.0 [18.2, 41.6] |
| Morphine group ($n$=10) | 427 [331, 550] | — | 15.2 [9.8, 16.9] | 75.0 [39.9, 90.0] |
| Difference between groups | | | | |
| Clonidine–saline | 414 [−423, 1264] | 0.35 | 6.1 [−7.6, 25 6] | 15.0 [−15.0, 15.0] |
| Morphine–saline | −944 [−1237, −502] | 0.002 | −15.9 [−23.4, −9.4] | 45.0 [15.0, 75.0] |
| Morphine–clonidine | −1364 [−1941, −489] | — | −20.7 [−42.5 −7.7] | 45.0 [0.0, 60.0] |

*Table 3* Baseline systolic arterial pressure and heart rate, change from baseline values at 60 and 150 min after administration of the test drug, and minimum values (mean (SD) [95% confidence intervals]). Differences between groups (clonidine – saline or morphine – saline groups) are also shown. The test drug was injected i.m. immediately after obtaining baseline values: saline, clonidine 150 μg or morphine 10 mg in 1 ml. Paracetamol was given at 60 min. *Data at 150 min were from seven patients

| | | Change from baseline | | |
|---|---|---|---|---|
| | Baseline (0 min) | 60 min −0 min | 150 min −0 min | Minimum value −0 min |
| Systolic arterial pressure (mm Hg) | | | | |
| Saline group ($n$=10) | 123 (13) | −7 (11) | −5 (9) | −12 (11) |
| Clonidine group ($n$=9*) | 124 (14) | −13 (14) | −16 (9) | −22 (8) |
| Morphine group ($n$=10) | 121 (12) | 1 (13) | −3 (9) | −9 (7) |
| Differences between groups for changes from baseline | | | | |
| Clonidine – saline | | −6 [−18, 6] | −12 [−20, −3] | −10 [−19, 0] |
| Morphine – saline | | 7 [−3, 18] | 2 [−7, 10] | 3 [−6, 12] |
| Heart rate (beat min$^{-1}$) | | | | |
| Control group ($n$=10) | 72 (5) | 4 (9) | 2 (14) | −1 (9) |
| Clonidine group ($n$=9*) | 74 (10) | 1 (9) | 0 (11) | −6 (9) |
| Morphine group ($n$=10) | 80 (8) | −1 (6) | −2 (7) | −6 (6) |
| Differences between groups for changes from baseline | | | | |
| Clonidine – saline | | −2 [−12, 7] | −2 [−14, 10] | −4 [−13, 4] |
| Morphine – saline | | −5 [−13, 2] | −4 [−14, 7] | −5 [−12, 2] |

(fig. 1, table 2). One-way analysis of variance showed that the AUC value was significantly different between the three groups ($P<0.001$); it was significantly smaller in the morphine group compared with the saline group ($P=0.002$; 95% CI for difference −1237 to −502 μg min ml$^{-1}$). In contrast, although AUC was greater in the clonidine group than in the saline group, this was not statistically significant (95% CI for difference −423 to 1264 μg min ml$^{-1}$).

Both arterial pressure and heart rate before injection of the test drug were similar in the three groups (table 3). Arterial pressure decreased in all the groups after injection of the test drug and was significantly lower after injection of clonidine than after saline (table 3). In one patient in whom clonidine had been given, arterial pressure decreased by more than 30%. Arterial pressure, however, returned to baseline values shortly after infusion of crystalloid fluid 500 ml. Changes in heart rate were not clinically significant (table 3).

*Table 4* Number of patients who were sedated before, and 60 and 150 min after administration of the test drug. The degree of sedation, if present, was always mild (score 2: see text) *Data at 150 min were from seven patients

| | Before | 60 min | 150 min |
|---|---|---|---|
| Saline group ($n$=10) | 0 | 1 (10%) | 4 (40%) |
| Clonidine group ($n$=9*) | 0 | 5 (56%) | 4 (57%) |
| Morphine group ($n$=10) | 0 | 3 (30%) | 7 (70%) |

Both clonidine and morphine appeared to have sedative effects. The degree of sedation, when present, was always mild (score 2) (table 4). The incidence of dryness of mouth was greater in the morphine group (eight patients (73%)) than in either the saline or clonidine groups (three patients in each group). Two patients in the morphine group had pruritus.

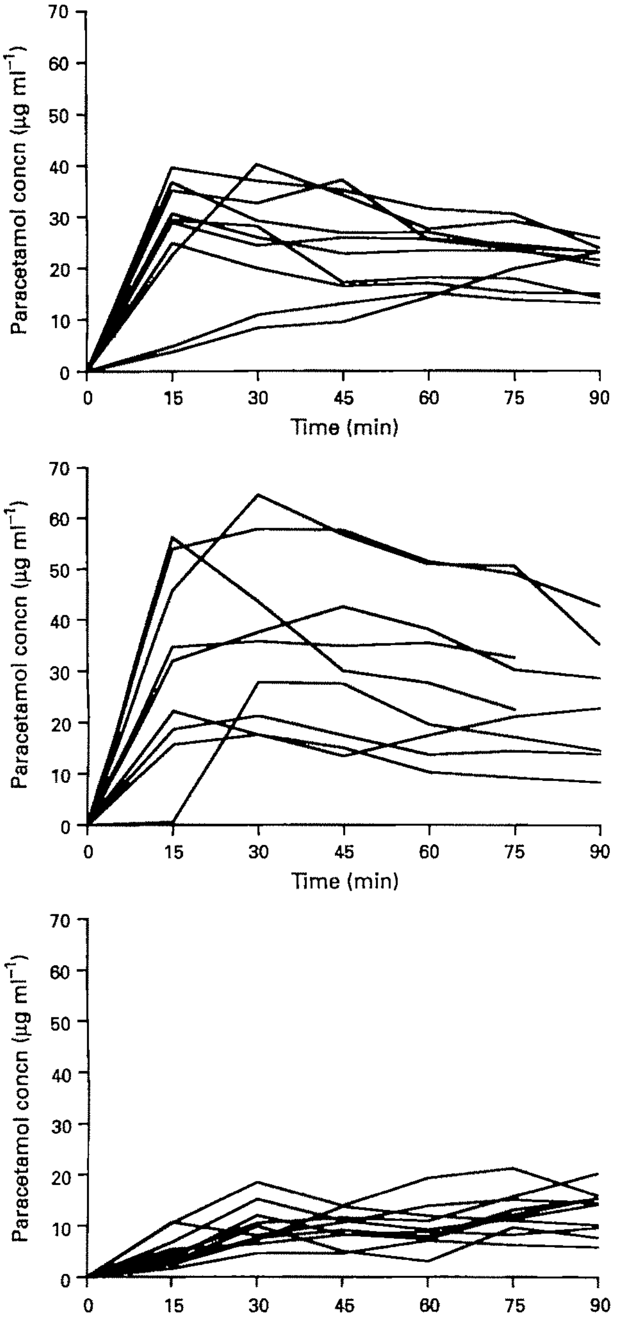

*Figure 1* Individual plots of plasma paracetamol concentration *vs* time after ingestion of paracetamol 1.5 g in 50 ml of water in the saline (top), clonidine (middle) and morphine (bottom) groups.

## Discussion

We have shown that clonidine 150 μg i.m. did not delay gastric emptying of liquids as did morphine. The median plasma paracetamol concentration in the clonidine group was greater than the upper 95% confidence limit of the median concentration in the saline group (fig. 1, table 2).

It was somewhat surprising to see higher plasma concentrations in some patients who had received clonidine. Alpha$_2$ adrenoceptor agonists inhibit contraction of the stomach caused by stimulation of cholinergic neurones,[23 24] although they do not inhibit contraction induced by exogenous acetylcholine.[23] However, they either have no effect or may have a stimulatory effect on the basal tone of the stomach.[24 25] In addition, $\alpha_2$ adrenoceptor agonists inhibit contraction of the pylorus.[26–28] In contrast, opioids increase pyloric pressure[29 30] which impedes emptying of gastric contents into the intestine.[31] Therefore, it might be possible that clonidine increased gastric emptying whereas morphine delayed it.

Paracetamol is not absorbed from the stomach but is well absorbed from the upper small intestine. It has been shown that there is a good correlation between the rate of absorption of paracetamol given orally and gastric emptying of liquids measured by a radio-isotope method.[17] Thus the rate of absorption of paracetamol indicates the rate of gastric emptying.[17 18] However, several factors, other than the rate of gastric emptying, may affect plasma paracetamol concentration.

First, if absorption of liquids from the small intestine is increased, the increase in plasma paracetamol concentration may be enhanced. In the isolated membrane of either the ileum or colon, $\alpha_2$ adrenoceptor agonists increase net transport of both fluid and electrolytes from the mucosal to the serosal side.[32 33] In intact animals, when secretion from the intestine is stimulated by chemical stimulation, $\alpha_2$ adrenoceptor agonists inhibit hypersecretion.[33 34] However, it is not clear if these drugs increase absorption of liquids, electrolytes and drugs from the small intestine during the unstimulated state in intact animals. In addition, opioids also increase absorption of liquids from the small intestine.[35–37]

Second, several factors affect hepatic enzyme activity and influence elimination of paracetamol that is metabolized by the liver: sex differences, ethnic differences, anticonvulsants, antituberculosis drugs, contraceptive pills and pregnancy.[38–43] It is not known if clonidine affects elimination of paracetamol. However, clonidine, about 50% of which is metabolized by the liver,[44] decreases elimination of sulphobromophthalein or bupivacaine from the liver and increases plasma concentrations.[45 46] Therefore, it is possible that clonidine interferes with elimination of paracetamol.

The decrease in arterial pressure after administration of clonidine might also have directly affected gastric emptying, or alternatively, might have decreased elimination of paracetamol by decreasing hepatic blood flow, leading to higher plasma paracetamol concentrations. In this study, the mean decrease in arterial pressure in the clonidine group was less than 20% compared with the saline group (table 3); in one patient in the clonidine group, arterial pressure decreased by more than 30%, but the duration of the decrease was short. In addition, calcium-channel blocking agents, at doses which would decrease arterial pressure, did not affect gastric emptying in humans, although arterial pressure was not measured in any study cited.[47–49] Therefore, the effect of this factor is likely to be minimum.

It seems reasonable to conclude that although the increase in plasma paracetamol concentration after administration of clonidine could have been caused by factors other than increased gastric emptying, it is unlikely that clonidine markedly delayed gastric emptying. Nevertheless, caution is required when the effect of either a test drug or conditions on gastric emptying is interpreted by differences in plasma paracetamol concentrations between groups, in particular when the difference is small.

Clonidine and morphine appeared to provide mild sedation. After administration of clonidine, patients became calmer, suggesting a possible anxiolytic effect of the drug. Morphine caused the well-known undesirable effects, such as vomiting, dryness of mouth and pruritus. In contrast, the incidence of these complications after clonidine was either less or none.

One of the concerns of the use of $\alpha_2$ adrenoceptor agonists as premedication or analgesia is hypotension. Arterial pressure decreased significantly after administration of clonidine but generally the decrease was either mild or moderate. The reference intervals represent the estimated range of values that include a certain percentage of the values among the population.[21] The 95% reference interval (mean±1.96) for the minimum arterial pressure after clonidine was 95–110 mm Hg. Although arterial pressure decreased by more than 30% in one of nine patients in our study, infusion of crystalloid fluid restored the pressure to baseline. Arterial pressure was within the normal range in this study; it is not known if clonidine markedly decreases arterial pressure more frequently in patients with hypertension or hypotension.

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# Effect of temperature during cardiopulmonary bypass on gastric mucosal perfusion

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**Summary**

The purpose of our study was to prospectively study the splanchnic response to hypothermic and tepid cardiopulmonary bypass (CPB) using alpha-stat management of arterial blood-gas tensions. Twenty-four patients for elective CABG surgery were allocated randomly to tepid (35–36 °C) or hypothermic (30 °C) bypass groups. Measurements were made at four times: (1) baseline, (2) stable during CPB (inflow temperature=nasopharyngeal temperature) 30 °C for hypothermic patients, bypass +20 min for tepid patients, (3) 10 min before the end of bypass, (4) after bypass, skin closure. Both groups demonstrated a significant reduction in gastric intramucosal pH (pH$_{im}$) from time 1 to time 4 and there was no difference in the incidence of a low pH$_{im}$ between the tepid and cold groups (4/12 *vs* 3/12; ns) at time 4. pH$_{im}$ was significantly lower in the tepid group at time 3 ($P$=0.03) but this discrepancy may have been because of an artefactually high pH$_{im}$ in the cold group. There was a significantly higher incidence of postoperative non-cardiac complications in patients who had a low pH$_{im}$ at time 4 ($P$=0.0008) Therefore, we conclude that although the temperature during CPB had a transient effect on pH$_{im}$ it is unlikely to be a major determinant in the pathogenesis of gut mucosal hypoperfusion after bypass. (*Br. J. Anaesth.* 1997; **78**: 000–000)

**Key words**

Gastrointestinal tract, pH. Gastrointestinal tract, mucosal perfusion. Heart, cardiopulmonary bypass. Surgery, cardiovascular Temperature, effect.

Despite advances in surgical technique, cardiopulmonary bypass (CPB) and anaesthetic management, non-cardiac complications occur frequently after surgery that requires CPB.[1] Global measures of oxygen consumption and delivery are not reliable predictors of regional organ dysfunction. Indirect measurement of gastric intramucosal pH (pH$_{im}$) is being used as a monitor of a tissue bed that is extremely sensitive to reduced peripheral perfusion and may be important in the pathogenesis of multiple organ dysfunction syndrome (MODS). An abnormally low pH$_{im}$ is common after CPB and a sensitive indicator of a poor outcome. The pathogenesis of the observed decrease in pH$_{im}$ remains poorly defined.

Hypothermia during cardiopulmonary bypass is thought to provide protection from ischaemic injury during CPB. The use of hypothermia during CPB has fallen out of favour in many institutions which has raised concerns regarding the potential for increased ischaemic injury in poorly perfused organs (e.g. the gut) during warm CPB. As a result, the purpose of our study was to prospectively compare the effect of hypothermic with tepid CPB on gastric mucosal pH.

## Patients and methods

After obtaining local Ethics Committee approval and informed consent, we studied 24 patients undergoing elective CABG surgery; patients were allocated randomly to a tepid (35–36 °C) or cold (30 °C) bypass group. Premedication comprised oral diazepam 0.1 mg kg$^{-1}$, oral methadone hydrochloride 0.1 mg kg$^{-1}$ and oral ranitidine 150 mg, 90 min before induction of anaesthesia. Anaesthesia was induced with midazolam 50–100 μg kg$^{-1}$ and fentanyl citrate 5–10 μg kg$^{-1}$, and maintained with a continuous infusion of midazolam 0.5 μg kg$^{-1}$ min$^{-1}$ and fentanyl 0.05 μg kg$^{-1}$ min$^{-1}$ throughout the study. Pancuronium was given as needed to maintain complete neuromuscular block.

Immediately after induction of anaesthesia a tonometer (Tonometrics Division Instrumentarium Corp., Helsinki, Finland) was inserted into the stomach and its position confirmed by injection of air down the nasogastric tube while auscultating over the epigastrium. The tonometer was primed for each measurement with 2.5 ml of 0.9% saline. The $P$CO$_2$ of the lumen of the stomach was measured indirectly by sampling the saline in the gas-permeable silicone

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balloon on the end of the tonometer after an equilibration period of more than 30 min and analysing the aspirate in a blood-gas analyser. At the same time an arterial sample was obtained to measure arterial bicarbonate concentration. $pH_{im}$ was calculated by inserting the values of gastric tonometer $P\text{CO}_2$ and arterial bicarbonate into a modified Henderson–Hasselbalch equation (eqn (1)), as described and validated previously.[2 3]

$$pH_t = 6.1 + \log_{10}(\text{arterial } [HCO^-{}_3] / P\text{CO}_2 (\text{tonometer}) \times K)$$

where $K$=time-dependent equilibration constant provided by the manufacturer. Measurements were made at four times: (1) baseline (before aortic cannulation); (2) stable during CPB (inflow temperature=nasopharyngeal temperature) 30 °C for cold patients, bypass +20 min for tepid patients; (3) before the end of bypass; and (4) after bypass, skin closure.

The perfusion apparatus consisted of a Cobe CML oxygenator (Cobe Laboratories, Lakewood, CO, USA) and a Sarns 7000 max pump (Sarns Inc, Ann Arbor, MI, USA). Non-pulsatile perfusion of 2.4 litre $\text{min}^{-1}$ $\text{m}^{-2}$ was maintained throughout the study. The pump was primed with a colloid and crystalloid solution designed to achieve a packed cell volume (PCV) of 0.18 or higher during extracorporeal circulation. Packed red blood cells were added when necessary to achieve the desired PCV. All patients underwent CPB with an ascending aortic cannula, an arterial filter and single stage venous cannula included in the system.

Blood-gas and tonometer saline analyses were made with a BGE IL1400 blood-gas electrolyte analyser (Instrumentation Laboratories, Lexington, MA, USA). Oxygen saturation and haemoglobin measurements were made on an IL482 co-oximeter (Instrumentation Laboratories, Lexington, MA, USA). Arterial carbon dioxide tension was maintained throughout CPB at 4.8–5.3 kPa (uncorrected for body temperature) and $Pa_{O_2}$ at 20–32 kPa.

Data management and analysis were performed using the SAS statistical system, version 6.08 for Windows on a 486-66 mHz Insight pc. All data were examined for normality of distribution, and group comparisons were made using parametric $t$ tests or non-parametric Wilcoxon rank sum tests as appropriate; descriptive data are presented as mean (SD). For comparisons of patient data, Wilcoxon's rank sum test of group equality was used. Cardiovascular variables were analysed by overall repeated measures analysis of variance followed by pairwise comparisons with baseline within groups (paired $t$ test) and also between groups (Wilcoxon rank sum test). $P<0.05$ was considered significant, without adjustment for multiple comparisons in the follow-up descriptive comparisons.

*Table 1* Patient data (mean (SD or range) or number)

| | Hypothermic group | Tepid group |
|---|---|---|
| *n* | 12 | 12 |
| Age (yr) | 58.5 (33–77) | 66.4 (56–81) |
| Weight (kg) | 99.2 (37.9) | 87.5 (14.9) |
| Sex (M/F) | 7/5 | 10/2 |
| Cross-clamp time (min) | 55 (20) | 37 (12) |
| CPB time (min) | 118 (40) | 83 (33) |

## Results

There was no difference between the hypothermic ($n$=12) and tepid ($n$=12) groups in patient characteristics, duration of bypass or aortic cross-clamp time (table 1). In the primary repeated measures analysis, there was no overall significant difference between the two groups in any of the cardiorespiratory variables, haemoglobin or $pH_{im}$ (table 2, fig. 1). Our sample size of 24 (12 per group) gave 80% power to distinguish a significant difference in $pH_{im}$ as small as 0.066 or larger between the groups.

In the follow-up descriptive comparisons there was a significant difference between the two groups in mean arterial pressure (MAP) at time 1 and nasopharyngeal temperature at times 2 and 3. Both groups demonstrated a significant increase in tonometer $P\text{CO}_2$ and a decrease in $pH_{im}$ from baseline to time 4. The increase in tonometer $P\text{CO}_2$ was independent of arterial $P\text{CO}_2$ which was unchanged in both groups. $pH_{im}$ was significantly lower in the tepid group at time 3 ($P$=0.03). The cold group had

*Table 2* Physiological variables. Times. (1) baseline, (2) stable (inflow temperature=nasopharyngeal temperature) 30 °C for cold patients, bypass +20 min for tepid patients, (3) before the end of bypass; (4) after bypass skin closure. $pH_{im}$ was calculated by substituting gastric $P\text{CO}_2$ and arterial bicarbonate measured from arterial blood-gas analysis into a modified Henderson–Hasselbalch equation (see patients and methods) Hg=haemoglobin content, MAP=mean arterial pressure, $Pa_{CO_2}$=arterial partial pressure of carbon dioxide, $pH_a$=arterial pH, $HCO_3$=arterial bicarbonate concentration, BE=arterial base excess, $CO_2$ gap=arterial carbon dioxide − splanchnic carbon dioxide $TONCO_2$=tonometer $P\text{CO}_2$ Data mean (SD). *$P<0.05$ between groups, †$P<0.05$ compared with baseline

| | Time 1 | | Time 2 | | Time 3 | | Time 4 | |
|---|---|---|---|---|---|---|---|---|
| Group | Cold | Tepid | Cold | Tepid | Cold | Tepid | Cold | Tepid |
| Temp. (°C) | 35.5 (1.3) | 35.4 (1.0) | 30 (0.4)† | 35.5 (0.5)* | 36.3 (0.3) | 35.8 (0.8)* | 35.8 (0.4) | 36.1 (0.6) |
| $pH_{im}$ | 7.42 (0.06) | 7.41 (0.06) | 7.42 (0.05) | 7.38 (0.04) | 7.43 (0.05) | 7.37 (0.06)* | 7.34 (0.06)† | 7.35 (0.05)† |
| $CO_2$ gap (kPa) | 0.16 (0.47) | 0.13 (0.97) | 0.17 (0.40) | 0.37 (0.52) | −0.25 (0.48) | 0.44 (0.61)* | 0.62 (0.52)† | 0.76 (0.75) |
| Hg (g $dl^{-1}$) | 13.0 (2.2) | 11.8 (2.5) | 8.7 (2.0)† | 8.8 (1.3)† | 8.6 (1.3)† | 8.5 (1.2)† | 10 (1.7)† | 9.1 (2.7)† |
| MAP (mm Hg) | 85 (10) | 73 (11)* | 71 (17) | 68 (11) | 65 (18) | 69 (12) | 76 (9) | 72 (14) |
| $pH_a$ | 7.42 (0.04) | 7.41 (0.04) | 7.41 (0.03) | 7.39 (0.04) | 7.39 (0.07) | 7.38 (0.05) | 7.37 (0.05) | 7.39 (0.04) |
| $Pa_{O_2}$ (kPa) | 32.4 (23.5) | 22.8 (8.1) | 27.6 (11.5) | 27.7 (10.5) | 24.7 (8.3) | 29.7 (11.9) | 18.4 (8.0) | 24.4 (13.9) |
| $Pa_{CO_2}$ (kPa) | 4.9 (0.53) | 5.1 (0.93) | 4.8 (0.53) | 5.2 (0.53) | 5.1 (0.53) | 5.1 (0.53) | 4.9 (0.53) | 4.9 (0.53) |
| $HCO_3$ (mmol $litre^{-1}$) | 24 (2) | 24 (3) | 23 (2) | 24 (2) | 23 (2) | 23 (2) | 22 (1) | 23 (2) |
| BE (mmol $litre^{-1}$) | 0.9 (2.2) | 0.02 (1.7) | −0.6 (2.3) | −0.4 (1.9) | −1.8 (1.9)† | −0.8 (2.2) | −2.7 (1.5)† | −1.5 (1.7) |
| $TONCO_2$ (kPa) | 5.2 (0.67) | 5.2 (0.67) | 4.9 (0.53) | 5.6 (0.67)* | 4.8 (0.53) | 5.5 (0.67)* | 5.6 (0.67)† | 5.7 (0.80)† |

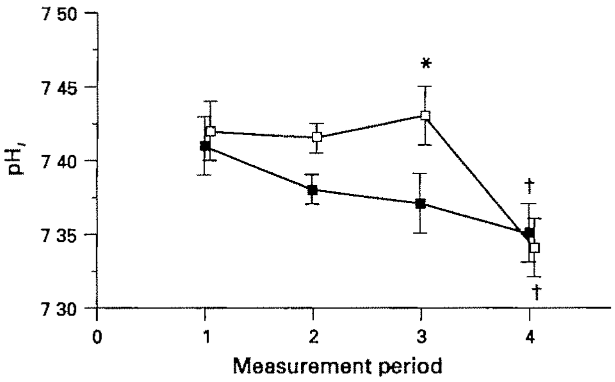

*Figure 1* Intramucosal pH ($pH_i$) at each of the measurement times in the cold (□) and tepid (■) CPB groups. $pH_{im}$ was calculated by substituting gastric $P\text{CO}_2$ and arterial bicarbonate measured from arterial blood-gas analysis into a modified Henderson–Hasselbalch equation (see patients and methods). Times. (1) baseline; (2) stable (inflow temperature = naso-pharyngeal temperature) 30 °C for cold patients, bypass +20 min for tepid patients; (3) before the end of bypass; (4) after bypass, skin closure. *$P<0.05$ between groups, †$P<0.05$ compared with baseline.

*Table 3* Postoperative complications. Time 4=after bypass, skin closure, LOS=length of stay, RML=right middle lobe

| $pH_{im}$ (time 4) | LOS | Complication |
|---|---|---|
| 7.32 | 10 | Post-pericardiotomy syndrome |
| 7 28 | 17 | Stroke |
| 7.29 | 12 | Wound infection, RML collapse, pneumonia |
| 7.29 | 18 | Wound cellulitis rt leg |
| 7.24 | 16 | Wound infection, debridement |

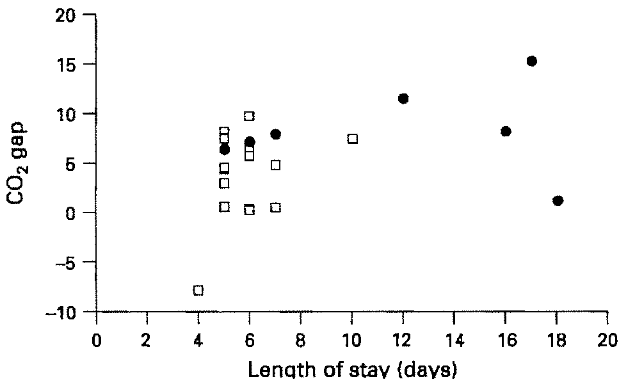

*Figure 2* Duration of hospital stay related to carbon dioxide ($CO_2$) gap and $pH_{im}$. $CO_2$ gap is the gap between gastric luminal $P\text{CO}_2$ and arterial $P\text{CO}_2$. Gastric hypercapnia relative to arterial $P\text{CO}_2$ is indicative of gut mucosal hypoperfusion. $pH_{im}$ is calculated by substituting gastric $P\text{CO}_2$ and arterial bicarbonate measured from arterial blood-gas analysis into a modified Henderson–Hasselbalch equation (see patients and methods). Logistic regression analysis examining the association between $pH_{im}$ (as a continuous measure) and risk of postoperative complications demonstrated a significant relationship ($P=0.0008$) between $pH_{im}$ at time 4 and prolonged hospital stay

a significant increase in base deficit compared with baseline at times 3 and 4. In both groups there was a significant decrease in haemoglobin concentration over time. Seven patients had an abnormally low $pH_{im}$ ($\leq 7.32$) by time 4. There was no difference in the incidence of a low $pH_{im}$ between the two groups (four in the cold group compared with three in the tepid group).

Of the seven patients who had a low $pH_{im}$ at time 4, four developed postoperative non-cardiac complications that resulted in an increased (greater than 7 days) duration of stay in hospital (table 3). One patient in the group that had a normal $pH_{im}$ at the end of surgery had an increased length of hospital stay. Logistic regression analysis, testing association between $pH_{im}$ (as a continuous measure) and risk of postoperative complications, demonstrated a significant relationship ($P=0.0008$) between $pH_{im}$ at time 4 and prolonged hospital stay (fig. 2).

## Discussion

This is the first prospective randomized study comparing gastric mucosal perfusion using tepid and cold bypass. The results indicate that the reduction in gastric mucosal perfusion after cardiac surgery was independent of the temperature during CPB. The warm group had a significantly lower $pH_{im}$ at time 3 during CPB. This was not evident after rewarming. The results of this study are consistent with previous studies that reported that decreases in gastric mucosal $pH_{im}$ are common after cardiac surgery and associated with prolonged hospital stay[2 4–7]

Kutilla, Niinikoski and Haglund examined the relationship between gastric $pH_{im}$ and peripheral tissue perfusion in patients after admission to the intensive therapy unit after hypothermic CPB.[8] They found that $pH_{im}$ decreased steadily over 4 h as the patient's core temperature increased to normal. From 4 to 8 h after operation, $pH_{im}$ increased again to normal. Over the same 8-h period they recorded a steady improvement in peripheral perfusion, as judged by subcutaneous and transcutaneous tissue oxygen tension, laser Doppler skin red cell flux and finger tip temperature, all measured on the same arm. They found no change in central haemodynamic state (including cardiac output). They attributed the changes to redistribution of blood flow after hypothermic CPB. Landow and colleagues studied patients during CPB to determine the relationship between gastric $pH_{im}$ and several other more invasively derived indices of splanchnic perfusion.[9] They found that mean $pH_{im}$ increased during the period of hypothermic CPB and then became abnormal only after rewarming. Gastric $pH_{im}$ correlated with hepatic venous lactate concentration and hepatic venous oxygen, suggesting supply-dependent oxygen deficit across the splanchnic bed. They proposed that with rewarming after hypothermic cardiopulmonary bypass there is regional oxygen consumption/delivery mismatch. This could have occurred in our patients and this postulate is consistent with our own $pH_{im}$ data in the hypothermic group. In a canine model, Ohri and colleagues demonstrated that during the rewarming phase of CPB there was jejunal mucosal hypoperfusion in spite of an increase in local blood flow.[10] They proposed a shunting phenomenon where blood flowed freely in the serosal but not mucosal layers. All of these studies suggest that temperature change is an important factor in the pathogenesis of gut mucosal hypoperfusion after CPB. Our results do not support this hypothesis because after cardiopulmonary bypass there was a significant decline compared with baseline but no difference between the two temperature groups.

Previous studies have suggested that the decrease in gastric pH to abnormal values is in proportion to the duration of CPB.[9 11] Suggested causes of impaired gut perfusion on CPB include occult hypovolaemia, ingestion of environmental endotoxin and release of endogenous vasoconstrictors during CPB.[6 12 13] During CPB large quantities of angiotension II are released.[14] In animal models, angiotension II was found to be a potent selective splanchnic vasoconstrictor.[15] Cardiopulmonary bypass also causes activation of platelets, neutrophils and inflammatory pathways.[16] Resulting microaggregate formation may cause microvascular occlusion and local reduction in oxygen delivery.[17] We have demonstrated previously that pre-emptive plasma volume expansion with a starch solution significantly reduces (but does not eliminate) gut mucosal hypoperfusion after bypass.[7] We have also noted that higher concentrations of endogenous endotoxin antibodies confer some protection against activation of inflammatory pathways and gut mucosal hypoperfusion.[18] Other investigators have tried to improve gut mucosal perfusion in the post-bypass period using cardioactive drugs such as dopexamine and dobutamine.[19] Despite increasing both whole body and splanchnic oxygen delivery, these drugs failed to improve gastric mucosal perfusion, as judged by the persistence of a low pH$_{im}$. One suggestion was that persistence of a gastric mural acidosis in the face of increased oxygen delivery was because of serosal shunting of blood in response to rewarming after cold CPB. We now believe that this is unlikely and think that microvascular occlusion secondary to formation of microaggregates or emboli is more consistent with the currently available data, as suggested in a study of retinal microembolism.[17]

The changes in pH$_{im}$ noted during hypothermic CPB in this and other studies may be artefactual as no allowance was made in the tonometric technique for the effects of temperature on carbon dioxide production, solubility and diffusion through tissues and the tonometer balloon. The tonometric technique is dependent on both aerobic and anaerobic production of carbon dioxide. The main reason for deliberately cooling patients during CPB is to reduce tissue metabolic rate and thus aerobic carbon dioxide production. Although this has not been studied systematically it seems reasonable to assume that background carbon dioxide production is reduced proportionally to temperature reduction and this calculated pH$_{im}$ is increased artefactually, independent of gut perfusion. In addition, reducing temperature increases tissue solubility of carbon dioxide and decreases diffusion through both tissues and the tonometer balloon. The manufacturers state that the device is intended for determination of "intramucosal pH of the gastric mucosal tissue at 37 °C". All of these factors would tend to give a falsely higher pH$_{im}$, irrespective of perfusion of the gastric mucosa. The possible artefactual effects of hypothermia on the tonometric readings have been poorly validated and are worthy of further investigation. This is a potential limitation of the interpretation of time 2 and 3 measurements in this study; however it should not affect conclusions drawn of the effect from beginning to end of CPB measurements.

There has been much recent debate on the validity of the calculation of pH$_{im}$ from gastric luminal $P\mathrm{CO}_2$ and systemic arterial bicarbonate.[6 20 21] Calculated pH$_{im}$ can be influenced by systemic acid–base disturbances independent of splanchnic perfusion. It has been suggested that a more specific measure of gut perfusion is the gap between gastric luminal $P\mathrm{CO}_2$ and arterial $P\mathrm{CO}_2$. Gastric hypercapnia relative to arterial $P\mathrm{CO}_2$ is indicative of gut mucosal hypoperfusion. In this study the significance of the results comparing the two groups was unaltered using calculated pH$_{im}$ or arterial to gastric $P\mathrm{CO}_2$ gap. However, one patient who had a poor outcome had an increased carbon dioxide gap but a normal pH$_{im}$ while another had a low pH$_{im}$ but a normal gap (fig. 2). Again, the significance of the results was unaltered but underlines the current suggestion of changing from calculation of pH$_{im}$ to reporting carbon dioxide gap. Calculated pH$_{im}$ is a sensitive indicator of tissue hypoperfusion whereas the carbon dioxide gap is a more specific indicator of gastric hypoperfusion.

The approach to arterial blood-gas management during hypothermic CPB remains controversial. In studies comparing pH and alpha-stat management, pH-stat management produced greater cognitive dysfunction after bypass, especially in patients requiring longer bypass times.[22 23] However, there are no human data comparing the two techniques in gut perfusion. It is the practice in our institution to use alpha-stat management of arterial blood-gas tensions.

The complications reported (table 3) occurred in patients in whom a low pH$_{im}$ developed. These data are consistent with the hypothesis that gut mucosal hypoperfusion may result in translocation of endotoxin, additional activation of inflammatory pathways and subsequent end-organ dysfunction.

We conclude that splanchnic hypoperfusion is common after CPB and associated with prolonged hospital stay. There was a lower pH$_{im}$ during warm CPB; this may have been because of an artefactually high pH$_{im}$ in the cold group. After CPB, using alpha-stat management of arterial blood-gas tensions, there was a significant reduction in pH$_{im}$ in both groups and the incidence of a low pH$_{im}$ and major complications were the same in both groups. Therefore, we conclude that temperature during CPB had no significant effect on the degree of gut mucosal hypoperfusion after CPB.

## Acknowlegement

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*British Journal of Anaesthesia* 1997; **78**: 39–43

# Non-invasive measurement of cerebral blood volume in volunteers

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**Summary**

Invasive techniques are used for conventional measurements of cerebral blood volume and there is a need for methods which are more readily applicable clinically. We studied 13 healthy volunteers using near infrared spectroscopy and transcranial Doppler sonography. Middle cerebral artery flow velocity (vmca) and changes in cerebral oxygenated haemoglobin ($HbO_2$), deoxygenated Hb (Hb), $HbO_2$+Hb (Hbdiff) and $HbO_2$+Hb (total haemoglobin; Hbt) were measured at baseline and during graded reduction in arterial oxygen saturation ($Sp_{O_2}$) to 85%, at hypo-, normo- and hypercapnia. Cerebral blood volume (CBV) values, calculated from regression lines of Hbdiff/$Sp_{O_2}$ and $HbO_2$/$Sp_{O_2}$ were 5.38 and 4.03 ml 100 $g^{-1}$ for the two methods, respectively. CBV varied directly with $FE'_{CO_2}$, with mean CBV reactivities of 1.25 and 1.06 ml 100 $g^{-1}$ $kPa^{-1}$, respectively. Changes in Hbt were not systematically related to changes in $FE'_{CO_2}$. An increase in vmca and reciprocal decrease in estimated cerebrovascular resistance were observed when oxygen saturation decreased to less than 90–93%. These results suggest that cerebral haemodynamics in *individual* subjects may be monitored non-invasively providing the methodology is modified to account for hypoxic vasodilatation. (*Br. J. Anaesth.* 1997; **78**: 39–43)

**Key words**

Hypoxia. Brain, blood flow. Brain, blood volume. Measurement techniques, near infrared spectroscopy

Changes in arterial oxygen and carbon dioxide tensions have important effects on the cerebral vasculature. Hyperventilation is commonly used to reduce cerebral blood volume (CBV) and control increased intracranial pressure during neuroanaesthesia and in neurosurgical critical care. While several studies have addressed the effects of changes in $Pa_{CO_2}$ on cerebral blood flow, few have addressed the effects of carbon dioxide changes on CBV because methodology for its measurement is not available widely and not applicable to routine monitoring of individual patients in clinical practice.

The aim of this study was to evaluate the use of non-invasive methods to estimate CBV using graded arterial hypoxaemia and changes in carbon dioxide tension. Changes in cerebral blood flow and CBV were estimated by non-invasive methods of monitoring using transcranial Doppler (TCD)[1] and near infrared spectroscopy (NIRS), a relatively new application of an existing technology which can be used to provide information on changes in the levels of cerebral oxygenated and deoxygenated haemoglobin, cerebral blood flow and volume.[2–9]

## Subjects and methods

After obtaining local research Ethics Committee approval and informed consent, we studied 13 healthy subjects (eight men), mean age 35 (range 22–57) yr.

The middle cerebral artery (MCA) was localized through the temporal window with the TCD probe (SciMed, Bristol, UK) and the sample depth volume altered until the trunk of the MCA was being insonated. This provided time-averaged mean measurements of MCA flow velocity (*v*mca). The NIRS probes (NIR 1000; Hammamatsu Photonics, Japan) were then attached to the forehead, 6 cm apart, on the same side as the TCD and secured by gauze wrapped around the head to prevent movement and interference from extraneous light. We used NIRS to measure cerebral concentrations of deoxygenated haemoglobin (Hb), oxygenated haemoglobin ($HbO_2$), the difference between oxygenated and deoxygenated haemoglobin (Hbdiff) and total haemoglobin ($Hb+HbO_2$). A plethysmographic non-invasive continuous arterial pressure monitor (Finapres; Ohmeda, UK) and a pulse oximeter probe (Multinex; UK) were attached to the fingers on the right hand. Fractional end-tidal carbon dioxide concentrations in expired air ($FE'_{CO_2}$) were measured using an infrared carbon dioxide analyser (Capnomac; Datex, UK).

After a period of stable baseline recording the subject was then asked to breathe air through a mouthpiece connected to a low resistance anaesthetic

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breathing system. After 3 min of baseline measurement, the subject was then given a hypoxic mixture of nitrogen in oxygen to gradually decrease oxygen saturation to 85%. After another 3 min of recording at baseline, carbon dioxide was added to the inspired gas mixture to increase the end-tidal carbon dioxide concentration to approximately 1.5 kPa above baseline at normoxia. Steady levels of hypercapnia were maintained for 3 min, after which the hypoxic mixture was re-introduced to gradually reduce $Sp_{O_2}$ to 85% during hypercapnia. Carbon dioxide was withdrawn from the inspired gas mixture, $Sp_{O_2}$ was allowed to normalize and the subject was then asked to hyperventilate aiming for an end-tidal carbon dioxide of 3.5 kPa. Each subject was held at stable hypocapnia for 3 min during which gradual desaturation was again repeated. After this, subjects breathed air until baseline $Sp_{O_2}$ and end-tidal carbon dioxide concentrations were re-established. The measured variables, oxygen saturation, end-tidal carbon dioxide, cerebral oxygenated and deoxygenated haemoglobin concentrations, CBV, arterial pressure and heart rate were averaged over 2-s epochs, down-loaded on to a lap-top computer and analysed using software developed for monitoring intracranial pressure and waveform analysis.[10] An example of the data output from one volunteer is shown in figure 1. As near infrared spectroscopy measures changes in cerebral haemoglobin from baseline values, negative values can appear on the display. When comparing data between individuals, values need to be indexed relative to baseline.

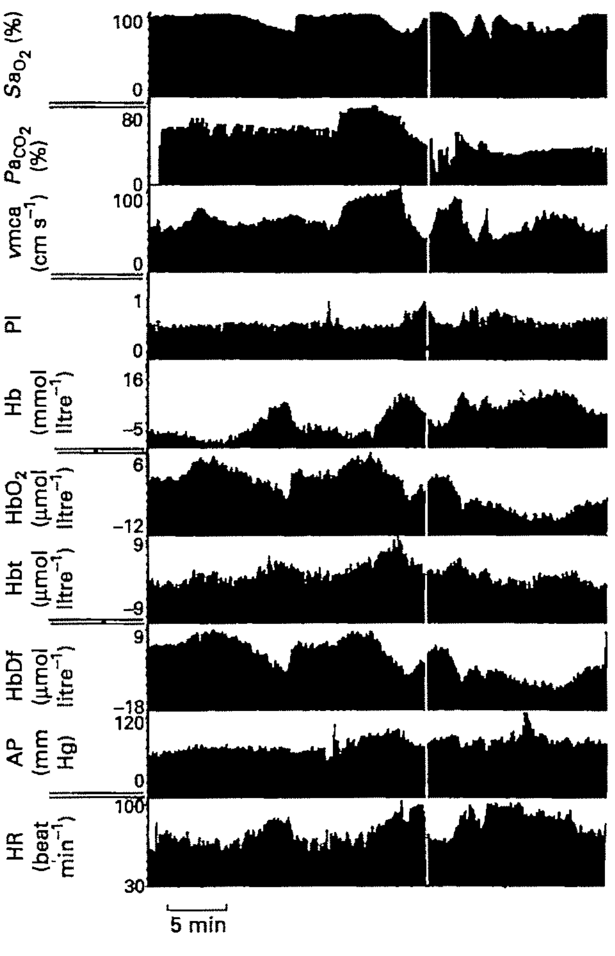

*Figure 1* Summary of part of the multichannel data download in an individual volunteer. $Sa_{O_2}$=arterial oxygen saturation; $Pa_{CO_2}$=end-tidal carbon dioxide concentrations; *v*mca=time averaged mean MCA flow velocity; PI=pulsatility index; Hb=deoxygenated haemoglobin; $HbO_2$=oxygenated haemoglobin; Hbt=total haemoglobin, HbDf=$HbO_2$ – Hb; AP=mean arterial pressure; HR=heart rate.

Regression lines of cerebral oxygenated haemoglobin $HbO_2$ and Hbdiff *vs* oxygen saturation ($Sp_{O_2}$) were plotted for each individual at the three carbon dioxide concentrations, and a value for the slope of $HbO_2/Sp_{O_2}$ calculated. Cerebral haemoglobin ($[Hb_{calc}]$) concentration was calculated using the formula described by Elwell and colleagues[9]:

$$[Hb_{calc}] \text{ (mmol litre}^{-1}) = \Delta[HbO_2]/\Delta Sp_{O_2}$$

The use of the Hbdiff value for this calculation increases the signal-to-noise ratio, but modifies the equation as follows:

$$[Hb_{calc}] \text{ (mmol litre}^{-1}) = \Delta[\text{Hbdiff}]/2 \times \Delta Sp_{O_2}$$

CBV was calculated from this using the following formula:

$$\text{CBV (ml 100 g}^{-1}) = K[\text{Hbcalc}]/Hb \times \text{CLVHR}$$

where *Hb*=large vessel haemoglobin concentration (assumed to be 15 g dl$^{-1}$). Haemoglobin concentration was not measured in individual subjects as all volunteers were healthy adults. This should have no effect on calculated values after indexing the data. CLVHR=Coefficient of the large to small vessel packed red cell ratio (assumed to be 0.69)[9] and *K*=a constant:

$$K = MW_{Hb} \times 10^{-3}/d_t \times 10$$

where $MW_{Hb}$=molecular weight of haemoglobin and $d_t$=tissue density.

Pooled data from all subjects were used to derive regression lines for the relationships between $FE'_{CO_2}$ and absolute CBV, and $FE'_{CO_2}$ and indexed CBV (indexed to calculated CBV at an $FE'_{CO_2}$ of 5.3kPa for each subject). Values of each variable were pooled for all subjects and plotted against $FE'_{CO_2}$ and a regression equation obtained. Regression lines with values less than 0.7 were not included. The slope of the regression line equalled carbon dioxide reactivity of CBV for the group. The second regression equation allowed expression of CBV reactivity as a percentage of baseline CBV, and compensated the contributions of individual variations in baseline CBV to variations produced in CBV reactivity. CBV reactivity was also calculated directly by indexing the change in Hbt to the change in $FE'_{CO_2}$.

The effect of changes in $FE'_{CO_2}$ on *v*mca was assessed by calculating *v*mca at an $FE'_{CO_2}$ of 5.3kPa for each subject, and indexing changes in *v*mca to this value.

## Results

Changes in mean arterial pressure during the course of these experiments were well within the limits of pressure autoregulation (MAP range 71–112 mm Hg). Steady state levels of $FE'_{CO_2}$ at normocapnia, hypercapnia and hypocapnia were achieved in nine of 13 subjects (mean 5.0 (SD 0.32), 6.3 (0.52) and 3.5 ( 0.32) kPa, respectively). Four subjects did not achieve steady state end-tidal carbon dioxide concentrations at one or more stages of the study and

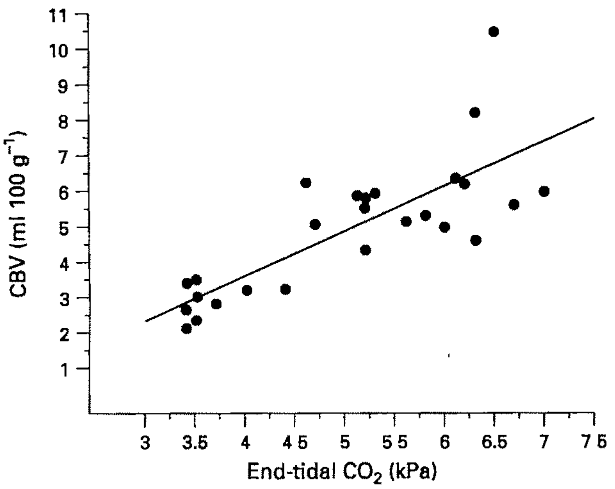

*Figure 2* Cerebral blood flow (CBV) calculated from the slope of Hbdiff *vs* $Sp_{O_2}$ during gradual arterial desaturation to 85%, in relation to $F\mathrm{E}'_{CO_2}$ values for all subjects. The regression equation for the relationship is CBV (ml 100 $g^{-1}$)=1.33+1.25 $F\mathrm{E}'_{CO_2}$ (kPa) ($r^2$=0.06, *P*=0.0001).

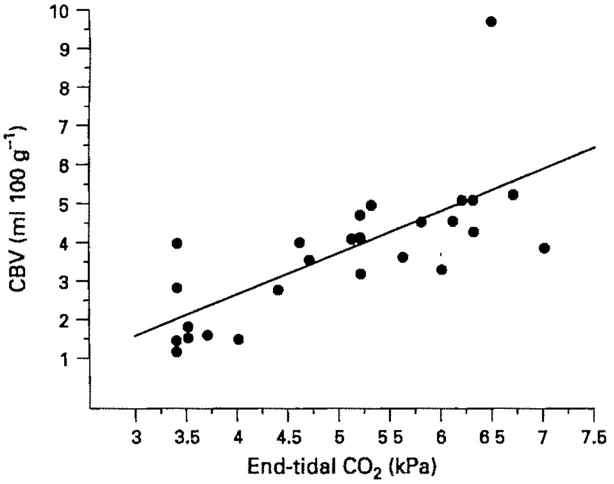

*Figure 3* Cerebral blood flow (CBV) calculated from the slope of $HbO_2$ *vs* $Sp_{O_2}$ during gradual arterial desaturation to 85%, in relation to $F\mathrm{E}'_{CO_2}$ values for all subjects. The regression equation for the relationship is CBV (ml 100 $g^{-1}$)=−1.61+1.06 $F\mathrm{E}'_{CO_2}$ (kPa) ($r^2$=0.51; *P*=0.0001)

were excluded. Data presented here are therefore from nine volunteers.

There were no significant or systematic differences in Hbt concentrations at normal levels of $Sp_{O_2}$ between any of the groups, and changes in Hbt were not significantly related to alterations in $F\mathrm{E}'_{CO_2}$.

CBV values were calculated from the $HbO_2/Sp_{O_2}$ and Hbdiff/$Sa_{O_2}$ regression slopes, and termed CBV(Hbdiff) and CBV($HbO_2$), respectively. CBV calculated by both methods was significantly related to $F\mathrm{E}'_{CO_2}$ ($r^2$=0.60 and 0.51, respectively; *P*<0.0001 for both), equating to CBV reactivities of 1.25 ml 100 $g^{-1}$ $kPa^{-1}$ (95% confidence interval (CI)= 0.8–1.7 ml 100 $g^{-1}$ $kPa^{-1}$) and 1.06 (95% CI=0.61–1.52) ml 100 $g^{-1}$ $kPa^{-1}$, respectively (figs 2 and 3). Mean calculated CBV values at $F\mathrm{E}'_{CO_2}$=5.3 kPa for the two methods were 5.38 (95% CI 5.12–5.64) ml 100 $g^{-1}$ and 4.03 (3.73–4.33) ml 100 $g^{-1}$, respectively. When changes in CBV with $F\mathrm{E}'_{CO_2}$ were indexed to calculated CBV at normocapnia ($F\mathrm{E}'_{CO_2}$=5.3 kPa) for each subject, there was a significant increase in the quality of fit for the regression line of CBV *vs* $F\mathrm{E}'_{CO_2}$ ($r^2$=0.67 and 0.66; *P*<0.0001, respectively) suggesting that at least some of the variability in CBV reactivity was the result of differences in baseline CBV (figs 4 and 5). CBV reactivities calculated from these figures suggested that CBV changed 22% and 25% from normocapnic values for each kPa change in $F\mathrm{E}'_{CO_2}$.

Compared with baseline values at normocapnia, mean *v*mca changed by 18 (14–21)% of normocapnic *v*mca for each kPa change in $F\mathrm{E}'_{CO_2}$ (fig. 6).

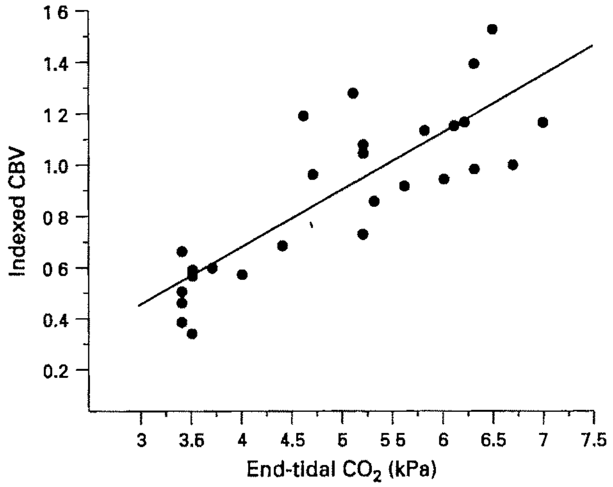

*Figure 4* Cerebral blood flow (CBV) calculated from the slope of Hbdiff *vs* $Sp_{O_2}$ during gradual arterial desaturation to 85%, in relation to $F\mathrm{E}'_{CO_2}$ values for all subjects. Regression equations were obtained for data from each individual subject and the CBV at normocapnia ($F\mathrm{E}'_{CO_2}$=5.3 kPa) calculated. All values of CBV were indexed to this value. The resulting line shows an improvement in fit ($r^2$=0.60 *vs* 0.67) and implies a 22% change in normocapnic CBV values for each kPa change in $F\mathrm{E}'_{CO_2}$

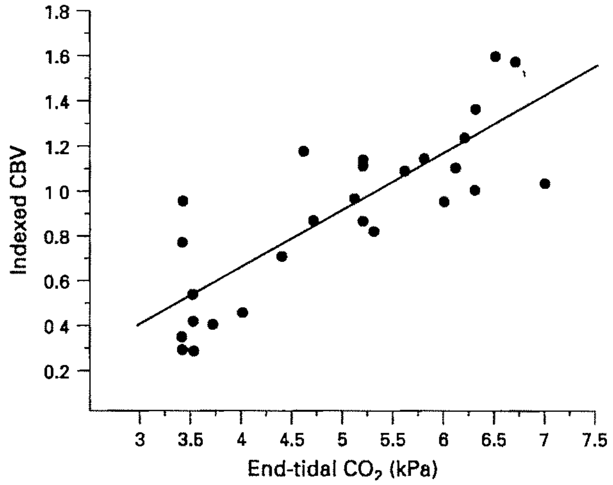

*Figure 5* Indexed cerebral blood flow (CBV) CBV calculated from the slope of $HbO_2$ *vs* $Sp_{O_2}$ during gradual arterial desaturation to 85%, in relation to $F\mathrm{E}'_{CO_2}$ values for all subjects Regression equations were obtained for data from each individual subject and the CBV at normocapnia ($F\mathrm{E}'_{CO_2}$=5.3kPa) calculated. All values of CBV were indexed to this value. The resulting line shows an improvement in fit ($r^2$=0.51 *vs* 0.66) and implies a 25% change in normocapnic CBV values for each kPa change in $F\mathrm{E}'_{CO_2}$.

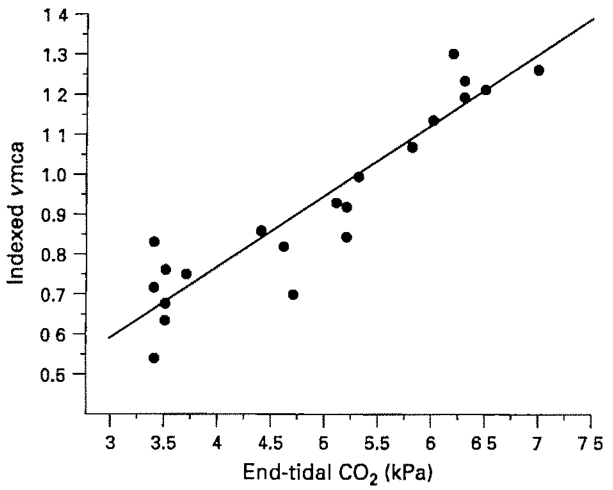

*Figure 6* Indexed flow velocity as a function of end-tidal carbon dioxide concentrations. Regression equations were obtained for data from each individual subject and *v*mca at normocapnia ($FE'_{CO_2}$=5.3 kPa) calculated. All values of CBV were indexed to this value. The resulting regression line ($r^2$=0.86; $P<0.0001$) implies an 18% change in normocapnic *v*mca values for each kPa change in $FE'_{CO_2}$.

## Discussion

Near infrared spectroscopy can provide information on changes in cerebral haemoglobin concentrations and might be expected to be a useful technique to study changes in CBV. Although CBV (and hence cerebral haemoglobin concentrations) would be expected to vary with changes in $Pa_{CO_2}$, we were unable to demonstrate significant changes in Hbt during normoxia at different levels of $Pa_{CO_2}$. However, calculated CBV reactivities from the slopes of Hbdiff/$Sp_{O_2}$ and $HbO_2$/$Sp_{O_2}$ were 1.25 and 1.06 ml 100 $g^{-1}$ $kPa^{-1}$, respectively, and calculated CBV at normocapnia for these two methods were 5.38 and 4.03 ml 100 $g^{-1}$. The discrepancy between CBV reactivity observed with these two methods and the absence of significant change in Hbt concentrations with $FE'_{CO_2}$ changes requires explanation.

It may be that the Hbdiff/$Sp_{O_2}$ and $HbO_2$/$Sp_{O_2}$ slope techniques are more robust methods of measuring CBV than direct measurement of Hbt. Brun and Griesen[8] used NIRS to measure CBF and CBV in neonates and found marked discrepancies between the two methods. CBV reactivity to changes in carbon dioxide was 0.89 ml 100 $g^{-1}$ $kPa^{-1}$ with the Hbdiff/$Sp_{O_2}$ slope method and 0.22 ml 100 $g^{-1}$ $kPa^{-1}$ with the Hbt technique. They attributed this to inaccuracies in the algorithms used to calculate CBV in each case, but suggested that the Hbt technique was less reliable. Their results for carbon dioxide reactivity of CBV using the slope method were similar to ours, but substantially different from other reports. Wyatt and colleagues[7] used changes in Hbt to estimate changes in CBV in response to alterations in $Pa_{CO_2}$ and reported a reactivity of 0.51 ml 100 $g^{-1}$ $kPa^{-1}$ (0.07 ml 100 $g^{-1}$ mm $Hg^{-1}$) in full-term neonates. Grubb and colleagues[11] used positron emission tomography and reported reactivities of 0.04 ml 100 $g^{-1}$ mm $Hg^{-1}$ (0.3 ml 100 $g^{-1}$ $kPa^{-1}$) and a CBV value of 3.6 ml 100 $g^{-1}$ at a $Pa_{CO_2}$ of 5.3 kPa in baboons. Elwell and co-workers[9] used the Hbdiff/$Sp_{O_2}$ slope technique and reported a CBV value of 2.85 ml 100 $g^{-1}$ in healthy adult volunteers. We were unable to find other measurements of changes in CBV with carbon dioxide concentrations in adults.

We observed a difference in the $HbO_2$/$Sp_{O_2}$ slope at different levels of $Pa_{CO_2}$ and the explanation suggested from the work of Elwell and colleagues[9] is that this represents a change in CBV. However, it is important to explore other causes for this phenomenon. One possible mechanism could be that the oxyhaemoglobin dissociation curve is shifted to the left as a result of respiratory alkalosis produced by hyperventilation, thereby decreasing the oxygen availability to tissues.[12] If this were an important effect, the rate at which oxygen was unloaded from haemoglobin in tissues with increasing arterial desaturation might be decreased during hypocapnia, thus contributing to a reduction in the gradient of the $HbO_2$/$Sp_{O_2}$ slope. The issue of whether or not hypocapnic changes in the haemoglobin–oxygen ($Hb–O_2$) dissociation curve contribute to tissue hypoxia remains unresolved. Cruz, Gennarelli and Hoffstad studied 37 brain injured patients with jugular venous monitoring during hyperventilation.[13] They concluded that the Bohr effect was irrelevant to cerebral oxygen availability during hypocapnia unless hypocapnia was profound (arterial pH>7.6). However, no direct information on the effect of $Pa_{CO_2}$ concentrations on the $Hb–O_2$ dissociation curve (e.g. $P_{50}$) was provided and this study primarily addressed the adequacy of oxygen delivery to the brain in "optimally ventilated" patients with head injury and abnormal cerebrovascular reactivity; any conclusions drawn from these data may not necessarily apply to hyperventilation in normal subjects with intact autoregulation. In our experiments, CBF appeared to increase during mild desaturation at hypocapnia in volunteers, suggesting that the threshold for hypoxic vasodilatation may have been breached, despite the literature suggesting a much lower $Sp_{O_2}$ value for initiation of this phenomenon.

The suggestion that hypocapnic vasoconstriction may cause cerebral hypoxia adequate to result in vasodilatation is supported by the findings of Alexander and co-workers[14] who showed a small increase in glucose metabolism and elevated lactate production during hypocapnia in lightly anaesthetized subjects. This implies that excessive hyperventilation may cause a critically reduced tissue $Po_2$ in that there is a shift from aerobic to anaerobic metabolism of glucose. Under such conditions, maintenance of tissue oxygen delivery can be achieved only by reversal of at least part of the hypocapnic vasoconstriction with resulting increases in CBF and CBV. This explanation is supported by the results of a separate study that we performed under the same experimental conditions[15] where we demonstrated significant decreases in estimated cerebrovascular resistance ($CVR_E$) and significant increases in *v*mca during graded arterial desaturation at $Sp_{O_2}$ values of 90%.

This discussion may provide a possible explanation for the discrepancies that we observed between our two measures of CBV reactivity. Conventionally, we would not expect to see alterations in CBF in response to reductions in oxygen saturation that we produced, as other studies[16–18] suggest a $Pa_{O_2}$ threshold for hypoxic vasodilatation of approximately 6.7 kPa. This translates to an arterial oxygen saturation of approximately 85%. However, the increases in *v*mca observed with mild arterial desaturation during hypocapnia suggests that hypoxic vasodilatation was present in our subjects. Under these conditions CBF and CBV would be increased and the requirements for calculating CBV from the Hbdiff/$Sp_{O_2}$ slope might no longer be satisfied.

In summary, our data suggest that if estimation of CBV is made using the Hbdiff/$Sp_{O_2}$ slope method then such measurements would be best made with $Sp_{O_2}$ swings between 93 and 100%. With modification of procedures to account for hypoxic cerebral vasodilatation, the non-invasive methods that we used deserve further investigation as non-invasive monitors of CBF and CBV in *individual* patients who have compromised cerebrovascular autoregulation or abnormal oxygen delivery–demand relationships, or both.

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# Use of modified fluid gelatin and hydroxyethyl starch for colloidal volume replacement in major orthopaedic surgery

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## Summary

We have compared 6% hydroxyethyl starch (HES 200/0.5) with 3% modified fluid gelatin (MFG) for volume replacement in major orthopaedic surgery and studied the effects on haemodynamic state, colloid osmotic pressure, blood clotting and plasma homeostasis. Using a controlled, randomized, single-blind clinical design, we studied 46 consecutive patients undergoing major elective orthopaedic hip surgery. The two groups were comparable in age, body weight and duration of surgery. Patients were maintained haemodynamically stable using both HES and MFG over the entire study. Fluid balance and colloidal replacement volumes were comparable in both groups (median perioperative infusion volume: HES 2500 ml, MFG 2400 ml). Laboratory variables were not clinically different. We conclude that both colloidal solutions were comparable in volume efficacy and effects on plasma oncotic pressure, clotting and plasma homeostasis. In the small number of patients studied, 6% HES 200/0.5 was found to be safe when administered in amounts corresponding to the currently accepted maximum daily dose in Germany and France of 33 ml/kg body weight and 2.0 g/kg body weight, respectively. (*Br. J. Anaesth.* 1997; **78**: 44–50)

**Key words**
Surgery, orthopaedic. Fluid balance. Fluids, i.v.

Synthetic colloids are used widely for replacement of blood loss during major surgical procedures. Defined blood components are transfused only when blood or plasma losses exceed the various limits set for replacement of blood components. The main reason for using colloidal volume replacements is to maintain the circulating blood volume by stabilizing plasma oncotic pressure in the perioperative period. At present, plasma substitutes based on dextran, gelatin and hydroxyethyl starch (HES) are available. The use of these colloids varies greatly between countries in Europe: while dextrans are preferred in Scandinavia, gelatin is the most frequently used synthetic volume replacement solution in the rest of Europe. Only in Germany has HES been the dominant colloid for more than 10 yr. Gelatin solutions are generally regarded as less efficient than HES preparations, although comparative clinical studies are rare.

The aim of this prospective, randomized study was to test if comparable haemodynamic stabilization could be achieved during major orthopaedic procedures using 3% modified fluid gelatin (MFG; mean molecular weight 30 000; Gelafundin) and 6% hydroxyethyl starch (HES 200/0.5, mean molecular weight 200 000, molar substitution 0.5; Hemohes) in the perioperative period, and to determine what quantities of colloid must be infused using a standardized therapeutic plan. In addition, we examined the effects on fluid balance, transfusion of blood products, blood clotting, plasma oncotic function, renal function and other laboratory variables.

## Patients and methods

After approval by the Ethics Committee, and having obtained informed consent, we recruited 48 patients between August 1992 and June 1994 in a randomized, single-blind clinical study. Forty-one of these patients were evaluable (withdrawal of consent ($n$=3) and blood loss too low because of limitation of the planned procedure ($n$=2)). It was not possible to conduct the study double-blind because of the different colours of the two solutions. In addition, gelatin produces foam on shaking and can therefore be distinguished easily from HES.

All patients required major orthopaedic hip surgery with an expected blood loss of >1000 ml. Exclusion criteria were haemoglobin concentration $\leq$11 g dl$^{-1}$, heart failure and coronary artery disease, previous myocardial infarction within the past 6 months, hypertension (>180 mm Hg systolic), impaired renal function (serum creatinine >130 μg litre$^{-1}$), pregnancy, known hypersensitivity to HES or gelatin, use of drugs that may specifically affect blood viscosity or diuresis and clotting disorders (as measured by thrombin time, Quick value and platelet count).

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We measured arterial pressure, heart rate, central venous pressure, packed cell volume (PCV), haemoglobin, platelet count, prothrombin time (Quick value), thrombin time, partial thromboplastin time, fibrinogen, serum concentrations of electrolytes ($Na^+$, $K^+$, total calcium, $Cl^-$), creatinine, urea, blood glucose, α-amylase, total protein, colloid osmotic pressure (COP) using an Osmostat 050 colloid osmometer (Gonotec; membrane exclusion size 20 000 Da, reference cell 0.9% NaCl) and plasma viscosity using a capillary viscosimeter.

Fluid input and output were monitored during and after surgery. Intraoperative blood loss was calculated from the estimated blood loss in compresses and towels and aspirated volumes (cell saver). The blood volume in drainage was measured after operation. Urine volume was measured using an indwelling catheter in the urinary bladder.

Arterial pressure, heart rate and central venous pressure were monitored continuously during surgery. Postoperative measurements were performed at 3, 6, 12 and 24 h after surgery. Laboratory variables were determined before induction of anaesthesia, every 2 h during surgery, at the end of operation, and 6, 12 and 24 h after operation. At the end of operation and after 6, 12 and 24 h, blood loss was determined and the input and output balance calculated. Urine volume was measured hourly during operation and 3, 6, 12 and 24 h after operation.

All patients were treated by the same anaesthetist (induction with etomidate or barbiturate, fentanyl and pancuronium; maintenance with continuous infusion of fentanyl and midazolam). A mixture of 66% nitrous oxide in oxygen was used with controlled ventilation of the lungs via a tracheal tube. Unfractionated heparin 5000 u. s.c. three times a day was given for postoperative thrombosis prophylaxis.

Fluid and volume replacement and transfusion of blood products were carried out using normal clinical criteria, standardized as follows: preoperative fluid deficit (20 ml $kg^{-1}$) was replaced by 50% in the first hour and by 25% after 2 h and 3 h by infusion of Ringer's acetate solution. Basal fluid replacement (3 ml $kg^{-1}$ $h^{-1}$) was also carried out using Ringer's acetate. Colloidal volume replacement was tailored according to intra- and postoperative haemodynamic variables (central venous pressure, heart rate, arterial pressure and systolic pressure variation), estimated blood loss and clinical status, using only gelatin or HES in the two groups. During operation, haemoglobin concentration was measured photometrically at 15-min intervals using a haemoxymeter (OSM 3, Radiometer). Results were available within 5 min. If haemoglobin concentration decreased to less than 8 g $dl^{-1}$ during surgery, packed red cells were transfused. After surgery haemoglobin concentration was maintained at 10 g $dl^{-1}$. If serum total protein concentration decreased to less than 4 g $dl^{-1}$, human albumin was transfused. If blood loss exceeded 1 litre, blood clotting variables were also analysed at regular intervals. Transfusion of clotting factors in the form of fresh frozen plasma (FFP) was not coupled with preset limits of coagulation factors because clinical experience failed to demonstrate a conclusive relation between global coagulation variables and a clinical bleeding tendency. Therefore, coagulation factors were transfused depending on clinical signs. FFP was administered if diffuse bleeding occurred. This plan was chosen because coupling transfusion of blood components to volume replacement using a rigid mathematical model (e.g. the Berner blood component scheme) was not appropriate for individual patients and had been shown to be impracticable in a pilot study.

All data are expressed as mean (SD). Because of the skewed and non-continuos distribution of fluid balance data, median and lower and upper quartiles were calculated. Between-group comparisons were made using the Mann–Whitney *U* test. The level of significance was $\alpha=0.05$. In order to show equivalence of colloid input, 90% confidence intervals were chosen in accordance with the α used. For presentation of fluid input and output data, box-and-whisker plots were used. The box contains 50% of the data (25–75% percentiles) and is crossed with a bar at the median. Vertical lines are drawn from each end of the box to the corresponding extreme. Mean values are indicated by a diamond.

## Results

There were no differences between groups in patient data. The types of surgical procedures were similar in the two groups (tables 1 and 2). The majority of patients underwent an exchange of a cemented total endoprosthesis (TEP).

Haemodynamic variables (systolic (SAP) and diastolic (DAP) arterial pressures, heart rate (HR) and central venous pressure (CVP)) were similar at the start of the study in both groups and there were no between-group differences during or after surgery. Patients in both groups remained haemodynamically stable (table 3).

PCV and haemoglobin concentrations (Hb) were initially low in both groups (table 4). With the chosen regimen for replacement of blood losses, PCV and Hb decreased during surgery in both groups to approximately 25% and 8.5 g $dl^{-1}$, respectively, and remained at these levels until the end of operation. After operation they stabilized at a slightly higher level (30% and 10 g $dl^{-1}$).

*Table 1* Patient data (mean (SD or range))

| | HES group | MFG group |
|---|---|---|
| *n* | 19 | 22 |
| Age (yr) | 56.9 (21–76) | 60 0 (24–80) |
| Height (cm) | 165 7 (9.6) | 165 6 (9 2) |
| Weight (kg) | 71.4 (11 2) | 67 0 (9.5) |
| Operation time (min) | 240 (80) | 237 (78) |

*Table 2* Operative procedures

| Operations | HES group | MFG group |
|---|---|---|
| TEP exchange | 11 | 9 |
| TEP implantation | 2 | 3 |
| Acetabulum exchange | 3 | 7 |
| Triple osteotomy | 3 | 2 |
| Partial pelvic resection | 0 | 1 |

*Table 3* Mean (SD) systolic (SAP) and diastolic (DAP) arterial pressures, heart rate (HR) and central venous pressure (CVP) before (Preop.), during (Intraop.) and after intervention in the hydroxyethyl starch (HES) and modified fluid gelatin (MFG) groups

| | | | | | Postoperative | | | |
|---|---|---|---|---|---|---|---|---|
| Group | Variable | Preop. | 2 h intraop. | End of op. | 3 h | 6 h | 12 h | 24 h |
| HES | SAP | 127 4 (19.7) | 101.0 (13.1) | 103.3 (13.2) | 120.9 (20.6) | 119.9 (21.1) | 120.6 (19.6) | 129.9 (21.0) |
| MFG | (mm Hg) | 124.1 (16.9) | 104.0 (17.5) | 107.7 (14.5) | 119.5 (24.5) | 119.4 (19.3) | 114.7 (11.4) | 122.5 (18.0) |
| HES | DAP | 78.1 (12.3) | 59.4 (11 0) | 60.7 (14.4) | 61.6 (11.4) | 58.9 (13.9) | 59.9 (14.0) | 62.6 (12.0) |
| MFG | (mm Hg) | 75 2 (10.3) | 61.4 (11.6) | 62.6 (10.0) | 60.3 (11.6) | 62.1 (8.5) | 57.7 (7.1) | 62 4 (10 8) |
| HES | HR | 82.1 (13.1) | 67.1 (9.5) | 70.7 (13.2) | 101.7 (18.1) | 97.1 (15.3) | 96.2 (14.1) | 85.8 (13.0) |
| MFG | (beat min$^{-1}$) | 80.2 (12 3) | 66.1 (8.1) | 66.5 (8.1) | 95.1 (21.6) | 95.4 (18.2) | 93.5 (14.0) | 88.4 (14.6) |
| HES | CVP | 2.9 (1.4) | 9.2 (3.6) | 10.1 (1.7) | 8.8 (2.5) | 9.1 (3.8) | 8.0 (3.8) | 6.7 (3.0) |
| MFG | (mm Hg) | 3.1 (1.8) | 9.2 (2.4) | 9.0 (2.6) | 8.3 (2.9) | 7.6 (2 8) | 7.9 (2.7) | 5.3 (1.5) |

*Table 4* Mean (SD) packed cell volume (PCV), haemoglobin (Hb) and total serum calcium ($Ca_{total}$) before (Preop.), during (Intraop ) and after intervention in the hydroxyethyl starch (HES) and modified fluid gelatin (MFG) groups. *$P<0.05$, **$P<0.01$ (group comparison)

| | | | | | | Postoperative | | |
|---|---|---|---|---|---|---|---|---|
| Group | Variable | Preop. | 2 h intraop. | 4 h intraop. | End of op. | 6 h | 12 h | 24 h |
| HES | PCV | 36.7 (4.8) | 26.1 (3.6) | 25.9 (5.8) | 26.4 (4.5) | 28.7 (4.4) | 28.7 (3.8) | 28.6 (3.4) |
| MFG | (%) | 36.8 (3 8) | 24.7 (3.3) | 24.1 (3.3) | 25 1 (4.1) | 31.3 (5.9) | 30.9 (4.3) | 30.6 (3.8) |
| HES | Hb | 12 4 (1.6) | 8.5 (1.0) | 8.7 (1.9) | 8.9 (1.5) | 9.6 (1.7) | 9.7 (1.2) | 9.7 (1.1) |
| MFG | (g dl$^{-1}$) | 12 5 (1.3) | 8.1 (1 2) | 8.0 (1.2) | 8.5 (1.3) | 10.6 (1.9) | 10.5 (1.4) | 10.4 (1.3) |
| HES | $Ca_{total}$ | 9.1 (0.4) | 7.6 (0.7) | 6.9 (0.3) | 7.2 (0.3) | 7 5 (0.6) | 7.8 (0.7) | 8.1 (0.4) |
| MFG | (mg dl$^{-1}$) | 9.2 (0.4) | 8.2 (0.3)** | 7.9 (0.4)** | 8.2 (0.3)** | 8.2 (0.4)** | 8.2 (0.3)* | 8.2 (0 3) |

*Table 5* Mean (SD) Quick value, thrombin time (TT), fibrinogen, platelets, creatinine, urea, total protein (TP), blood glucose and α-amylase concentrations before (Preop.), during (Intraop.) and after intervention in the hydroxyethyl starch (HES) and modified fluid gelatin (MFG) groups. *$P<0.05$, **$P<0.01$ (group comparison)

| | | | | Postoperative | | |
|---|---|---|---|---|---|---|
| Group | Variable | Preop. | End of op. | 6 h | 12 h | 24 h |
| HES | Quick value | 95.2 (6.5) | 63.0 (12 4) | 74.6 (14.4) | 76.2 (11.6) | 77.4 (10.7) |
| MFG | (%) | 95.9 (6.1) | 61.2 (9.5) | 76.5 (9.6) | 78.0 (8.1) | 75.3 (9.0) |
| HES | TT (s) | 14.8 (1.8) | 16.1 (2.1) | 16.0 (1.9) | 16 1 (3.5) | 15.8 (3.2) |
| MFG | | 14.9 (1.2) | 16 8 (1.6) | 16.9 (1.5) | 15.7 (1.4) | 15.6 (2.5) |
| HES | Fibrinogen | 293.4 (79.8) | 138.2 (47.8) | 177.6 (51.7) | 218.7 (52.4) | 313.3 (64.7) |
| MFG | (mg dl$^{-1}$) | 286.8 (63.1) | 141.2 (33.8) | 194.3 (35.6) | 240.2 (30.8) | 323.2 (50.9) |
| HES | Platelets | 239 5 (41 7) | 109 2 (41.8) | 128.9 (51 8) | 127.0 (47.8) | 135.1 (49 8) |
| MFG | ($10^3$ ml$^{-1}$) | 249.1 (50.0) | 123.2 (48.5) | 138.8 (60.6) | 143.8 (60.5) | 140 0 (59.2) |
| HES | Creatinine | 71 (18) | 62 (18) | 62 (9) | 71 (18) | 71 (18) |
| MFG | (μmol litre$^{-1}$) | 80 (18) | 71 (9) | 71 (9) | 71 (9) | 71 (9) |
| HES | Urea | 15.0 (4.2) | 13.9 (3.8) | 13.4 (4.4) | 12.6 (5.1) | 12.1 (4.9) |
| MFG | (mg dl$^{-1}$) | 18.0 (6.8) | 15.9 (5.3) | 14.9 (4.6) | 14.0 (4.7) | 12.7 (4.3) |
| HES | TP | 6.6 (0.8) | 3.4 (0.4) | 4.4 (0.6) | 4.8 (0.8) | 5.0 (0.7) |
| MFG | (g dl$^{-1}$) | 6.8 (0.5) | 4.0 (0.3)** | 4.8 (0.5)* | 4.9 (0.4) | 4.9 (0.4) |
| HES | Blood glucose | 5.1 (1.0) | 6.4 (2.1) | 9.0 (2.1) | 9.1 (2.3) | 7 7 (1.8) |
| MFG | (mmol litre$^{-1}$) | 5.0 (0.7) | 5.6 (1.0) | 9.4 (1.9) | 9.3 (1.7) | 7.5 (1.7) |
| HES | α-Amylase | 20.4 (7.4) | 22.3 (28.0) | 55.3 (80.9) | 66.4 (81.7) | 53.7 (50.1) |
| MFG | (iu litre$^{-1}$) | 19.1 (6.5) | 10.2 (4 2)** | 16.3 (9.5)** | 19.0 (11.6)** | 19 3 (11.1)** |

Serum concentrations of sodium and potassium varied slightly and remained within the reference ranges throughout the study. During surgery there was a significantly more pronounced reduction in total calcium concentration in the HES group compared with the gelatin group (table 4). Values in the HES group remained significantly lower up to 12 h after operation.

The Quick value decreased in both groups at the end of operation to approximately 60% and PTT was prolonged (57 s). By 6 h after surgery both variables had returned to normal (table 5). Platelet count decreased in both groups proportionally to blood loss and colloid volume transfused at the end of the operation, to approximately 50% of baseline, and remained at this level after operation. None of the other variables showed any clinically relevant changes or differences between groups.

Creatinine and urea concentrations, and urine excretion were similar in both groups. Blood glucose concentrations increased continuously in both groups, reaching a maximum 6–12 h after operation (approximately 9 mmol litre$^{-1}$) with a trend towards normalization by 24 h after operation. α-Amylase concentrations increased after operation in the HES group to 2.5–3 times baseline values and differed significantly at all times (6, 12, 24 h after operation) from those in the gelatin group.

Total protein (TP) concentration changed to a similar extent in both groups and decreased during operation within 2 h to approximately 60% of baseline and then diminished only slightly until the end of

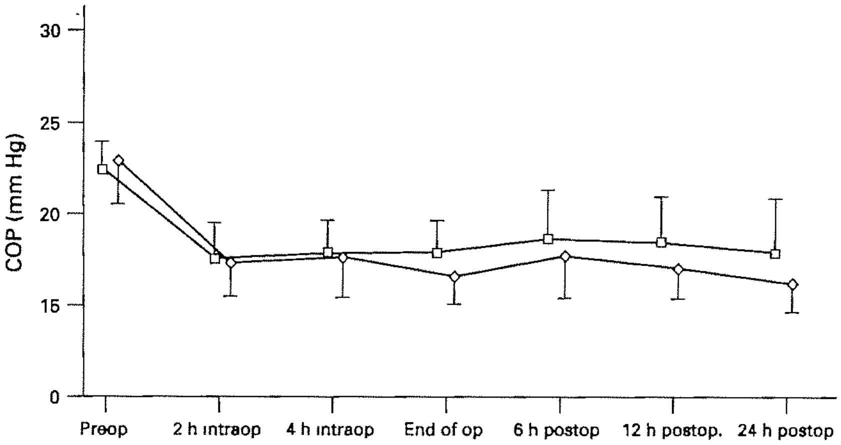

*Figure 1* Colloid osmotic pressure (COP) in the hydroxyethyl starch (□) and modified fluid gelatin (◇) groups (mean, SD), before operation (Preop.), 2 and 4 h during operation (intraop.), at the end of operation and 6 h, 12 h and 24 h after operation (postop.)

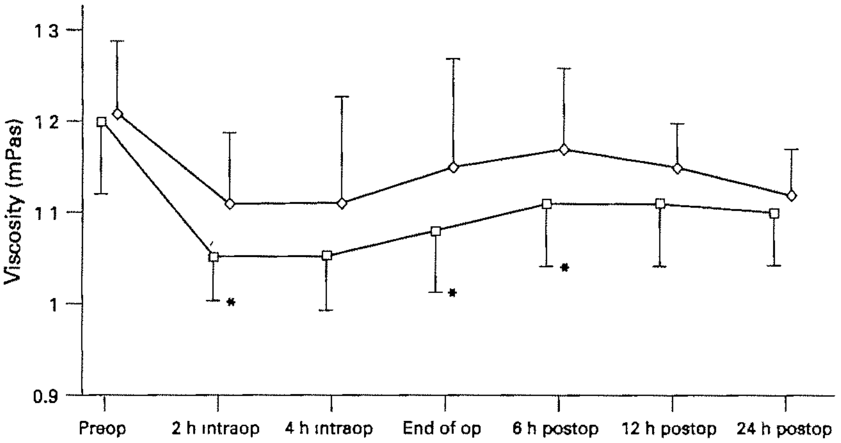

*Figure 2* Plasma viscosity in the hydroxyethyl starch (□) and modified fluid gelatin (◇) groups (mean, SD), before operation (Preop.), 2 and 4 h during operation (intraop.), at the end of operation and 6 h, 12 h and 24 h after operation (postop.) $^*P<0.05$ (group comparison).

operation (table 5). After operation, values stabilized in both groups at about the lower limit of the reference range (5 g $\text{dl}^{-1}$). However, TP values were significantly higher in the gelatin group than in the HES group at the end of operation and 6 h after operation. Plasma oncotic pressure (COP) decreased in both groups within 2 h to approximately 75% of baseline and stabilized at this level after operation with infusion of colloids (fig. 1). There were no significant differences in this variable between the groups. Plasma viscosity (PV) decreased during surgery in both groups in parallel with increasing dilution; the reduction was more marked in the HES group (fig. 2). There were significant between-group differences at 2 h after the start of surgery, at the end of operation and 6 h after operation.

Fluid input and output balances were similar in both groups. Statistical analysis confirmed that both products were equivalent with respect to the amount of colloid infused during operation; median and 90% confidence intervals of the median were the same in both groups (1900–2500 ml and 1500–2500 ml, $\alpha=0.05$). Median postoperative colloid infusion was 500 ml in both groups whereas the upper limit of the 90% confidence interval in the gelatin group was higher than in the HES group (1000 ml and 500 ml) indicating slightly higher postoperative volume requirements in the gelatin group (fig. 3).

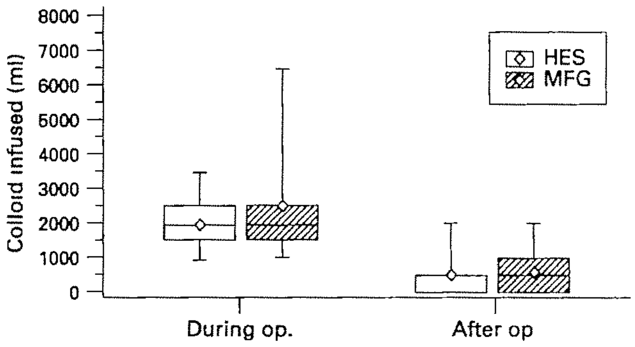

*Figure 3* Amount of colloid infused during operation and the first 24 h after operation in the hydroxyethyl starch (HES) and modified fluid gelatin (MFG) groups. The box contains 50% of the data (25–75% percentiles) and is crossed with a bar at the median Vertical lines are drawn from each end of the box to the corresponding extreme. Mean values are indicated by the diamond.

Total median volume of colloids infused during operation and during the first 24 h after operation was 2500 ml in the HES and 2400 ml in the MFG group; 90% confidence intervals were 1500–2500 ml in the HES group and 2000–3000 ml in the MFG

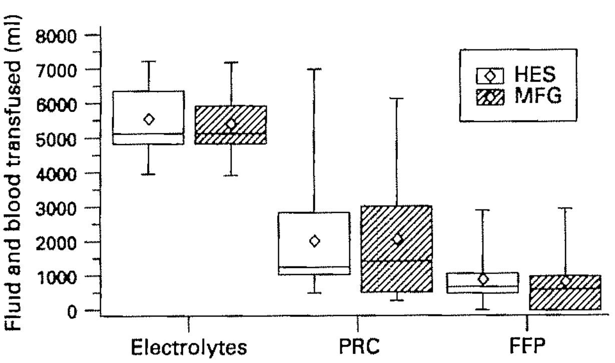

*Figure 4* Amount of perioperative electrolyte input and blood components transfused (packed red cells (PRC) and fresh frozen plasma (FFP))in the hydroxyethyl starch (HES) and modified fluid gelatin (MFG) groups. The box contains 50% of the data (25–75% percentiles) and is crossed with a bar at the median. Vertical lines are drawn from each end of the box to the corresponding extreme. Mean values are indicated by the diamond.

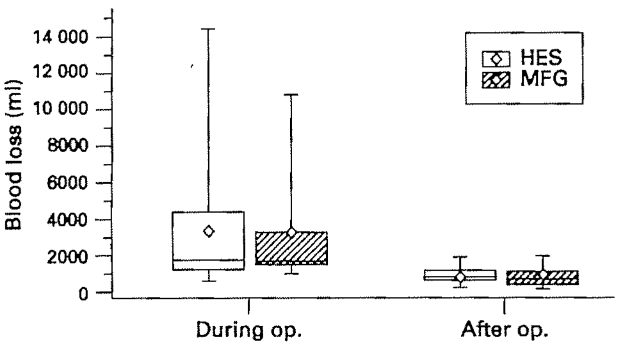

*Figure 5* Intra and postoperative blood losses in the hydroxyethyl starch (HES) and modified fluid gelatin (MFG) groups. The box contains 50% of the data (25–75% percentiles) and is crossed with a bar at the median. Vertical lines are drawn from each end of the box to the corresponding extreme. Mean values are indicated by the diamond.

group. However, there were no significant differences between groups, as indicated by the *U* test ($P$=0.52). Additional analysis of a subgroup of 10 patients in each group, whose operations lasted longer than 4 h, showed a trend towards increased colloid requirements in the gelatin group during operation (median volume infused 2.5 *vs* 1.9 litre; ns).

There was no difference in electrolyte infusion and use of blood products (packed red cells, fresh frozen plasma) (fig. 4).

Urine excretion was comparable in both groups during and after operation (median volume: HES 250 ml and 3620 ml *vs* MFG 290 ml and 3265 ml). The same was true for blood losses during and after operation (HES 1800 ml and 840 ml *vs* MFG 1750 ml and 775 ml) (fig. 5).

There were no allergic reactions to the infused substances in any patient.

## Discussion

Patients were recruited into this study only if they were undergoing major hip surgery. This condition was fulfilled as shown by the mean duration of operation of 4 h and the median perioperative blood loss of 2.6 litre in both groups.

Regarding the criteria for evaluation of the efficiency of colloidal volume replacement solutions, various pharmacological and clinical terms have been used as synonyms, including volume effect, volume efficacy, duration of action, duration of volume effect, (elimination) half-life and intravascular retention time. The most reliable variable for comparison purposes is the plasma elimination half-life or concentration half-life ($T_{1/2}$) defined as the time required for the concentration of a colloid in blood to decrease to 50% of its initial peak value. However, various factors affect this value, such as the rate of infusion, method of infusion (hypervolaemic or normovolaemic infusion), concentration of solution used and choice of observation period, and these have led to marked differences in published values. Thus various values for the intravascular half-life of similar HES solutions (HES 200/0.5; HES 264/0.45) have been reported in the scientific literature, ranging from 2.7 to 22 h.[1 2] The aim of this study was therefore to compare the clinical effects (haemodynamic stabilization, infusion volume required) of two standard colloids in major orthopaedic procedures under clinical conditions and using standardized infusion regimens.

Infusion of two volume replacement solutions was tailored to haemodynamic variables, estimated blood loss and clinical status. Invasive monitoring with a Swan–Ganz catheter was not indicated in these patients because of the associated risks. The same anaesthetist undertook all operations and a high degree of standardization of volume replacement was achieved.

There were no significant differences between groups with regard to circulation variables either before induction of anaesthesia or during or after operation. Haemodynamic variables showed that stabilization of the circulatory system was achieved over the entire study using infusion of both 3% MFG and 6% HES 200/0.5. Similar volumes of gelatin and HES were required during and after operation, while both the initial volume effect and plasma elimination half-life of HES are generally thought to be higher than those of MFG. At the same time, there were no noteworthy differences in the use of electrolytes and blood products or in blood loss and urine output. Only in patients with a duration of surgery of 4 h or more with correspondingly greater median blood loss (>2.6 litre) was a slight increase in requirements (~25%, corresponding to 500 ml) apparent in the gelatin group, but this could not be confirmed statistically. Thus both volume replacements fulfilled the criteria for efficient medium-term volume replacement.

There are few previous comparative studies of the efficacy of gelatin and HES. Beards and colleagues[3] found a comparable increase in pulmonary capillary wedge pressure, cardiac output and arterial oxygen transport in intensive care patients within 30 min after infusion of 500 ml of 4% MFG and high molecular weight starch (6% HES 450/0.7). They concluded from their study that the initial effects of succinylated gelatin and HES on haemodynamics and oxygen transport did not differ. Furic and colleagues[4] chose a pragmatic method in their prospective study of 987 patients. They could not confirm that 3.5% dextran 40 was more efficient than 3% MFG, as presumed on the basis of their pharmacological data. The same volumes of both colloids were used during the study. The aim of the study by Bérard and colleagues[5] was to determine if the theoretical advantages of HES compared with MFG in terms of duration of action operate in clinical practice and lead to a reduction in the volume required to maintain normovolaemia in critically ill patients. Although a slightly smaller number of HES units was infused, this was not significantly different from the number of units of MFG infused per patient (4.29 *vs* 5.02 u.). However, a highly significant difference was seen in the mean cost of volume replacement per patient. The use of HES multiplied the cost per patient by 1.72.

PCV decreased in both groups during operation to approximately 25%, while values of 30% were maintained after operation. These low PCV and haemoglobin values were well tolerated in all cases.

In contrast with gelatins, all HES solutions have a recommended upper dose limit because of their effects on coagulation factors, platelets and fibrinoformation. The dose limit was defined in the past on the basis of the volume infused, irrespective of the concentration of the solution. Recently, German and French licensing authorities have accepted that the upper dose limit of starches with a molar substitution of 0.5 should be defined by the amount of active substance administered. Thus in those countries it is now possible to infuse 20 ml/kg body weight per day of the 10% and 33 ml/kg body weight per day of the 6% solution, corresponding to HES 2 g/kg body weight per day.

The global clotting variables, which were additionally affected by perioperative administration of heparin, did not differ between the two groups. No patient showed dramatically altered values or clinically relevant bleeding tendency, and blood loss and transfusion volumes were comparable. This is not unexpected for gelatin as it is generally accepted that gelatin solutions do not have any specific effect on clotting, apart from the dilutional effect.[6] In contrast, highly substituted HES preparations (HES 200/0.62; 450/0.7) affect factor VIII complex to a greater extent than can be explained by dilution.[7] Bleeding complications have been reported, predominantly after infusion of large quantities or in association with repeated administration, especially in neurosurgical patients.[8–12] The results of this study in which a mean of 27 ml $kg^{-1}$ was infused over the intraoperative and 24-h postoperative period, with 10 patients receiving 6% HES 200/0.5$\geq$30 ml $kg^{-1}$ and seven patients $\geq$40 ml $kg^{-1}$, are in agreement with other investigations, in which various mean molecular weight HES preparations with a molar substitution of up to 0.5 apparently affected clotting to a much lesser degree.[13–16]

Apart from α-amylase, serum chemistry variables did not differ significantly between groups. The increase in α-amylase activity after infusion of HES is a well recognized phenomenon and is caused by formation of an enzyme–substrate complex between α-amylase and HES, with delayed elimination because of its size.[17] The increase in amylase does not signify pathology, but would be important in the differential diagnosis of suspected pancreatic disease. The stress response and related hormonal changes caused hyperglycaemia in both groups after operation, with no significant differences between them.

Apart from serum total calcium, electrolyte concentrations remained in the normal range. The decrease in total calcium in both groups can be explained by the known "rule of thumb" whereby a decrease in albumin concentration of 1 g $dl^{-1}$ is accompanied by a decrease in serum total calcium of 0.8 mg $dl^{-1}$.[18] The significantly higher values in the gelatin group compared with the HES group are probably because gelatin, in contrast with HES, contains calcium 1.4 mmol $litre^{-1}$, approximately the same as physiologically ionized calcium. Studies by Vogt, Schönberger and Kilian[19] have confirmed that HES does not specifically affect ionized calcium, even at higher doses.

Total protein (TP) and colloid osmotic pressure (COP) were similar in both groups. The significantly higher TP concentrations in the MFG group at the end of operation can be explained by the fact that gelatin is a polypeptide and participates in the biuret reaction for total protein determination.

COP values were similar throughout the observation period. The initial decrease in COP in both groups from approximately 22 to 17 mm Hg within the first 2 h after the start of operation was caused by infusion of approximately 20 ml $kg^{-1}$ of electrolyte solution for fluid replacement and consequent dilution. Values in both groups were then stable at this level for up to 24 h after operation.

Plasma viscosity decreased significantly compared with baseline values in both groups, solely because of the increasing haemodilution during the course of the operation. Presumably because of its additional specific effect on blood rheology, values in the HES group were significantly lower at 2 h after the start of operation, at the end of operation and 6 h after operation.

In summary, despite their different pharmacological properties, similar amounts of both solutions were required to achieve haemodynamic stabilization in patients throughout the course of the study. Fluid balance was similar in both groups. Only with operations lasting more than 4 h and median blood losses of more than 2.6 litre did the shorter plasma elimination half-life of gelatin solution cause increased requirements of about 25%, although this difference could not be confirmed statistically. HES 200/0.5 (6%) does not, therefore, have a significantly greater volume effect than 3% MFG in the procedures investigated here. There were no noteworthy differences in the effects on plasma oncotic pressure, blood clotting or plasma homeostasis. Restricted to the small number of patients, 6% HES 200/0.5 was found to be safe when administered in amounts corresponding to the currently accepted maximum daily dose in Germany and France of 33 ml/kg body weight, and 2.0 g/kg body weight, respectively.

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# Cardiorespiratory changes during gynaecological laparoscopy by abdominal wall elevation: comparison with carbon dioxide pneumoperitoneum

A. CASATI, G. VALENTINI, S. FERRARI, R. SENATORE, A. ZANGRILLO AND G. TORRI

## Summary

We have studied the cardiorespiratory changes produced by abdominal wall elevation (AWE) or carbon dioxide pneumoperitoneum (PN) in 20 women undergoing gynaecological laparoscopy. Arterial pressure, heart rate, lung/chest compliance and blood-gas tensions were measured 10 min after induction of general anaesthesia (T0), 10 min after abdominal distension in the supine position (T1) and 10 min after the Trendelenburg position was assumed (T2). Visual analogue scores for pain were recorded 1 and 6 h after the end of surgery. We found that lung/chest compliance was reduced significantly in group PN at T1 and T2 compared with both T0 and group AWE. Diastolic arterial pressure increased significantly in group PN at T1 and T2 compared with both T0 and group AWE, while it remained unchanged in group AWE. Arterial $P\text{CO}_2$ increased significantly only in group PN after pneumoperitoneum, while oxygenation was almost unchanged in both groups. AWE patients had greater abdominal pain 1 h after surgery. Six hours after surgery pain was similar in the two groups. These data indicate that abdominal wall elevation reduced pulmonary compliance less than a pneumoperitoneum in patients undergoing gynaecological laparoscopy. (*Br. J. Anaesth.* 1997; **78**: 51–54)

**Key words**
Surgery, laparoscopy. Carbon dioxide, pneumoperitoneum. Cardiorespiratory system, effects.

Laparoscopic abdominal surgery has been used increasingly in the past years for gynaecological surgery, cholecystectomy and more complex and difficult surgical procedures (e.g. vagotomy, herniorrhaphies, antireflux procedures, splenectomy, bowel resection).

The limited skin incision with laparoscopic procedures is usually associated with less postoperative pain and faster recovery.[1 2] Carbon dioxide pneumoperitoneum is the common method used to obtain abdominal distension for laparoscopy. Some complications such as hypercapnia and acidosis,[3] gas embolism,[4] pneumothorax, subcutaneous emphysema[5] and deep venous thrombosis[6] have been reported after carbon dioxide pneumoperitoneum. These complications may adversely affect patient outcome, especially in those with cardiac or respiratory disease.[7]

Alternatives to carbon dioxide pneumoperitoneum, helium and nitrous oxide pneumoperitoneum, have been studied: these gases avoid the increase in $Pa_{\text{CO}_2}$ and acidosis but do not resolve problems related to the increase in intra-abdominal pressure.[8 9]

Many methods of abdominal wall elevation have been developed for laparoscopy.[10 12] The Hanon technique allows for elevation of the abdominal wall ventrally, using an inflatable balloon or a fan retractor inserted into the peritoneal cavity through the base of the umbilicus. The balloon is connected to an automated mechanical lifting arm attached to the operating table. This system is designed to provide 13.6 kg or less of lift to the anterior abdominal wall, which approximates to the pressure provided by 1.95 kPa (15 mmHg) of pneumoperitoneum.[10] Abdominal wall elevation should theoretically reduce the negative effects on the diaphragm and abdominal great vessels caused by pneumoperitoneum.

The aim of this study was to compare the effects of carbon dioxide pneumoperitoneum with abdominal wall lift using a mechanical retractor device in patients undergoing gynaecological pelvic surgery.

## Patients and methods

With the approval of the local Ethics Committee and informed consent, we studied 20 women, ASA I, undergoing gynaecological laparoscopy for ovarian surgery.

Premedication comprised diazepam 5 mg orally and atropine 0.5 mg i.m., 30 min before induction of anaesthesia. After a 18-gauge i.v. cannula was inserted into the forearm, anaesthesia was induced with fentanyl 0.001 mg $\text{kg}^{-1}$ i.v. and thiopentone 5 mg $\text{kg}^{-1}$ i.v. Vecuronium 0.1 mg $\text{kg}^{-1}$ i.v. was given to facilitate tracheal intubation with a cuffed tube.

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Anaesthesia was maintained with 1–1.5% end-tidal isoflurane in an oxygen-enriched air mixture ($FI_{O_2}$=0.5) to maintain arterial pressure and heart rate within acceptable ranges. Intermittent positive pressure ventilation (IPPV) was applied using a Drager–Cato volume cycled ventilator, with an inspiratory flow rate of 25 litre min$^{-1}$, ventilatory frequency 12 bpm, tidal volume 10 ml kg$^{-1}$ and an inspiratory:expiratory ratio of 1:2. Ventilatory variables were not changed during the study.

Intraoperative monitoring included continuous ECG (lead II), non-invasive arterial pressure using an automated cuff, pulse oximetry, inspired oxygen fraction, end-tidal carbon dioxide concentration, end-tidal isoflurane concentration, airway pressure and minute ventilation.

Static compliance of the whole respiratory system (lung/chest wall compliance ($CPL_{RES}$)) was calculated by dividing expired tidal volume by static pressure (plateau pressure) after a 1-s inspiratory pause. To evaluate $\dot{V}/\dot{Q}$ mismatching, we calculated the ratio of arterial oxygen to inspired oxygen partial pressure ($Pa_{O_2}/FI_{O_2}$) as an index of pulmonary shunt,[13] and arterial to end-tidal carbon dioxide gradient, as an index of dead space.[14]

Patients were allocated randomly to receive abdominal distension by standard carbon dioxide pneumoperitoneum (group PN) or by the abdominal wall elevation device (group AWE). Carbon dioxide pneumoperitoneum was created using a Veress needle inserted into a small intra-umbilical incision. An electronic variable-flow insufflator terminated flow when an intra-abdominal pressure of 1.6 kPa (12 mm Hg) was reached. A 10-mm trocar was inserted in place of the needle to provide and maintain insufflation adequate for surgery. A video laparoscope was then inserted through the same trocar and the operative field was seen. In group AWE, an inflatable ring-shaped retractor was introduced into the peritoneal cavity (mesogastrium) via a small incision at the base of the umbilicus, using the Hanon technique, and then inflated.[10] The retractor was attached to an automated mechanical arm and the abdominal wall was elevated using 13.6 kg of tension to provide adequate vision of the operating field. The laparoscope was then inserted into the peritoneal cavity via the umbilical incision and through the hole present in the inflatable retractor to see the pelvic and abdominal organs. Positive pressure insufflated gases were not necessary for surgery.

Patients were then placed in a 30° Trendelenburg position. Heart rate (HR), systolic (SAP) and diastolic (DAP) arterial pressures, and static lung/chest compliance ($CPL_{RES}$) were recorded 10 min after induction of general anaesthesia before abdominal insufflation or wall elevation (T0), 10 min after abdominal distension or carbon dioxide insufflation (T1) and 10 min after Trendelenburg positioning (T2). At the same time, arterial blood was obtained for measurement of blood-gas tensions (IL BGM 1312; Instrumentation Laboratory, Lexington, MA, USA). All measurements were made before surgery was started.

At 1 and 6 h after the end of surgery, the intensity of abdominal pain was recorded using a visual analogue score (VAS 10 cm).

Data were collected and analysed using a statistical software package (StatView II SE, Abacus Concepts Inc., Berkeley, CA, USA). Analysis of variance for repeated measures with Sheeffé and Dunnet's tests of multiple comparison, Mann–Whitney test and chi-square test were used to asses changes over time both within and between groups. $P<0.05$ was considered significant. Data are reported as mean (SD) or median (range) for ordinal data.

## Results

Patient data are shown in table 1. Patients with preoperative hypotension or cardiopulmonary disease were excluded from the study. There were no

*Table 1* Characteristics of patients undergoing laparoscopy by carbon dioxide pneumoperitoneum (PN) or abdominal wall elevation (AWE). (Mean (SD) or range)). No significant differences between groups

| | PN (*n*=10) | AWE (*n*=10) |
|---|---|---|
| Age (yr) | 38.5 (26–48) | 44.0 (25–51) |
| Weight (kg) | 55.2 (9.0) | 59.2 (9.9) |
| Height (cm) | 164 (4.3) | 163 (3.9) |

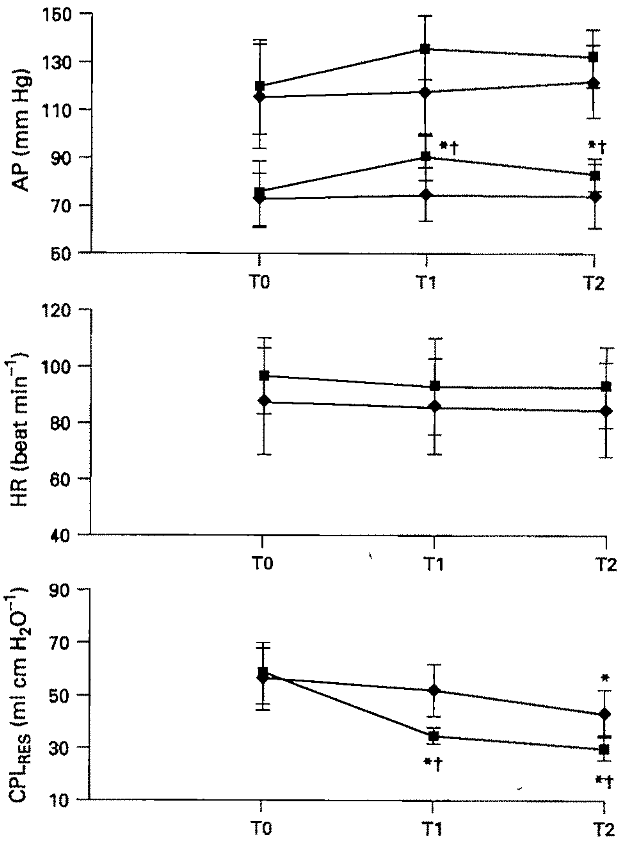

*Figure 1* Non-invasive arterial pressure (AP—systolic and diastolic), heart rate (HR) and lung/chest compliance ($CPL_{RES}$) measured 10 min after induction of general anaesthesia (T0), 10 min after abdominal distension or pneumoperitoneum (T1), and 10 min after Trendelenburg positioning (T2), in patients undergoing gynaecological laparoscopy by carbon dioxide pneumoperitoneum (■) or abdominal wall elevation (◆). *$P<0.05$ *vs* T0; †$P<0.05$ *vs* abdominal wall elevation.

*Table 2* Arterial pH, ratio of arterial oxygen to inspired oxygen partial pressure ($Pa_{O_2}/FI_{O_2}$), arterial to end-tidal carbon dioxide gradient (grad. $CO_2$) and arterial carbon dioxide partial pressure ($Pa_{CO_2}$) measured 10 min after induction of general anaesthesia (T0), 10 min after abdominal distension or pneumoperitoneum (T1), and 10 min after Trendelenburg positioning (T2), in patients undergoing gynaecological laparoscopy by carbon dioxide pneumoperitoneum (PN) or abdominal wall elevation (AWE) (mean (SD)). *$P<0.05$ *vs* T0

| | T0 | T1 | T2 | ANOVA |
|---|---|---|---|---|
| pH | | | | |
| AWE | 7.41 (0.04) | 7.40 (0.03) | 7.39 (0.04) | 0.330 |
| PN | 7.45 (0.04) | 7.39 (0.05) | 7.36 (0.05) | |
| $Pa_{O_2}/FI_{O_2}$ | | | | |
| AWE | 428 (116) | 464 (114) | 414 (103) | 0.114 |
| PN | 460 (175) | 534 (87) | 429 (98) | |
| Grad. $CO_2$ (kPa) | | | | |
| AWE | 0.27 (0.3) | 0.29 (0 31) | 0.33 (0.28) | 0.803 |
| PN | 0.28 (0.14) | 0.39 (0.27) | 0.30 (0.22) | |
| $Pa_{CO_2}$ (kPa) | | | | |
| AWE | 4.70 (0.40) | 4.79 (0.25) | 4.88 (0.32) | 0.221 |
| PN | 4.71 (0.39) | 5.18 (0.59)* | 5.55 (0.74)* | |

*Table 3* Visual analogue scores (VAS) for abdominal pain recorded 1 h and 6 h after the end of pneumoperitoneum (PN) and abdominal wall elevation (AWE) laparoscopy

| | PN ($n$=10) | AWE ($n$=10) | $P$ |
|---|---|---|---|
| VAS 1 h (cm) | 3.5 (2.2) | 5.5 (1.7) | 0.03 |
| VAS 6 h (cm) | 3.6 (2.4) | 3.9 (2.7) | 0.19 |

perioperative complications caused by anaesthesia or surgery.

Mean baseline HR was similar in both groups and did not change significantly during the study ($P$=0.26) (fig. 1). In group PN, DAP increased significantly after abdominal insufflation and after Trendelenburg positioning compared with both before insufflation (T0) and group AWE ($P$=0.04 and 0.02, respectively). SAP did not change significantly in either group during the study ($P$=0.11).

In the pneumoperitoneum group, lung/chest compliance decreased significantly after (T1) compared with before insufflation (T0) ($P$=0.01) and with group AWE ($P$=0.0001); there was a further reduction in $CPL_{RES}$ when the Trendelenburg position was assumed (T2) compared with both T0 ($P$=0.01) and group AWE ($P$=0.0006) (fig. 1). In AWE patients, lung/chest compliance did not change after abdominal elevation (T1) compared with values after induction (T0) ($P$=0.25), but it was significantly reduced after Trendelenburg positioning compared with T0 values ($P$=0.005). Compliance was significantly higher in group AWE compared with group PN both at T1 and T2 ($P$=0.0001 and 0.0006, respectively).

There were no significant changes in pH after abdominal distension and positioning (table 2). $Pa_{O_2}/FI_{O_2}$ and arterial to end-tidal carbon dioxide gradient did not change significantly after insufflation or abdominal lift or after Trendelenburg positioning in both groups (table 2). In contrast, $Pa_{CO_2}$ increased significantly in group PN after pneumoperitoneum ($P$=0.02) with a mean difference compared with group AWE of approximately 0.665 kPa (5 mm Hg), 10 min after Trendelenburg positioning (table 2).

One hour after the end of surgery, patients treated with the abdominal wall retraction procedure had greater abdominal pain than group PN ($P$=0.03). None of the patients received postoperative analgesic drugs and the nociceptive stimulus was short-acting; 6 h after surgery there were no significant differences in abdominal pain between the two groups (table 3).

## Discussion

The two different techniques used for laparoscopy produce a difference in diaphragm displacement and consequently lead to different degrees of reduction in functional residual capacity (FRC) in the two groups of patients during anaesthesia. Respiratory system compliance was reduced significantly using the pneumoperitoneum technique. Changes in respiratory compliance in this study were in agreement with previously reported data.[15] Another significant reduction in respiratory system compliance was caused by Trendelenburg positioning.[16]

In the AWE group, airway pressure and respiratory system compliance were almost unaffected by abdominal wall distension. When Trendelenburg position was used, respiratory system compliance was lower than values measured after induction of anaesthesia; values of $CPL_{RES}$, however, were significantly higher at this time in the AWE compared with the PN group.

Despite the relevant effects on lung/chest compliance, in this study we did not observe a significant difference in gas exchange in the two groups. In group PN, only $Pa_{CO_2}$ increased progressively because of its rapid absorption into the circulation via the peritoneum. Our data were obtained 10 min after abdominal distension and then 10 min after Trendelenburg positioning. This time interval might have been insufficient to produce effects on pulmonary gas exchange; consequently, the decrease in FRC, produced by reduction in compliance, could be expected to worse oxygenation in group PN after a prolonged observation time.

Carbon dioxide load, with its direct and indirect haemodynamic effects,[17] together with known increased cardiac afterload produced by intra-abdominal pressure elevation,[18] might be the determinant of the increase in diastolic arterial pressure in group PN. These modifications may lead to an increase in myocardial work and myocardial oxygen consumption.

It is known that carbon dioxide pneumoperitoneum produces an increase in central venous pressure by forcing blood from the abdominal organs into the central venous reservoir[19,20] and a high preload reduces coronary flow by decreasing coronary artery perfusion caused by increased ventricular wall stress.[21]

The abdominal wall elevation method, avoiding the increase in intra-abdominal pressure, might produce less effects on afterload and preload than pneumoperitoneum laparoscopy, further reducing the risks associated with laparoscopic procedures, especially in patients with poor cardiovascular reserve.

One hour after the end of surgery, group AWE had greater abdominal pain than the pneumoperitoneum group. This difference was probably a result of the smaller area of abdominal wall on which traction is applied in AWE compared with PN patients: in carbon dioxide pneumoperitoneum, abdominal distension involves all of the abdominal wall. Moreover, visual analogue scores were similar in the two groups 6 h after surgery. We believe that, unless statistically significant, the difference found 1 h after surgery is not clinicaly relevant in the postoperative management of patients.

Our data indicated that during gynaecological laparoscopy, abdominal wall elevation did not affect the respiratory system and gas exchange, reduced the negative effects on the cardiorespiratory system produced by pneumoperitoneum and may have improved the risk/benefit ratio of laparoscopic techniques.

Our patients were all young, relatively healthy females, undergoing short duration surgical procedures: they tolerated well pneumoperitoneum and the Trendelenburg position. The physiological effects of prolonged carbon dioxide insufflation into the peritoneum, combined with variations in patient positioning, have a major impact on cardiorespiratory function in elderly patients, with pre-existing cardiac or respiratory disease, undergoing surgical procedures with a longer duration than gynaecological laparoscopy. Further studies are required in these different groups of patients. Nevertheless, we believe that this technique of abdominal wall lifting and gasless laparoscopy should be advocated. The potential benefits of abdominal wall retraction may be useful for patients undergoing laparoscopic upper abdominal procedures of longer duration, in the reverse Trendelenburg position, and particularly when the patients are elderly with co-existing cardiac or respiratory disease, or both.

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LABORATORY INVESTIGATIONS

# Isoflurane increases the uptake of glutamate in synaptosomes from rat cerebral cortex

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## Summary

We have studied the effect of increasing concentrations of isoflurane on high- and low-affinity uptake of L-glutamate using synaptosomes from rat cerebral cortex. In the high-affinity uptake range, 0.5% isoflurane had no effect on uptake velocity, while 1.5% and 3.0% isoflurane caused an increase in mean *V*max to 131 (SEM 54) and 210 (103) % of control, respectively. There was no significant change in the $K_m$ value. *V*max and $K_m$ values for low-affinity uptake of L-glutamate were unchanged by 1.5% isoflurane. These results provide evidence for an isoflurane-induced increase in high-affinity uptake of glutamate into presynaptic terminals. This effect may contribute to a reduction of transmitter in the synaptic cleft and thereby decreased excitatory synaptic transmission. (*Br. J. Anaesth.* 1997; **78**: 55–59)

**Key words**
Anaesthetics volatile, isoflurane. Nerve, transmission Nerve, neurotransmitters. Nerve, synaptosome. Rat.

As early as 1906, Sherrington reported that chloroform blocks reflex activity in the spinal cord at lower concentrations than those needed to inhibit impulse propagation along nerve fibres.[1] Later studies have shown that other inhalation agents depress excitatory synaptic transmission in the superior cervical ganglion[2] and in various parts of the central nervous system, including the spinal cord,[3] cuneate nucleus,[4] olfactory bulb,[5] olfactory cortex[6 7] and dentate area.[8]

Isoflurane, a halogenated methyl-ethyl-ether, is used widely because of its advantages compared with older volatile anaesthetics. In the rat hippocampus, isoflurane inhibits excitatory signal transduction by depression of the activity in thin unmyelinated, afferent fibres,[9] reduction of excitatory synaptic transmission[10 11] and hyperpolarization of the postsynaptic neurone.[12 13]

The effect on excitatory synaptic transmission seems quantitatively to be the most important.[10 14] Synaptic transmission may be depressed by drug-induced reduction in the release of the transmitter from the presynaptic terminal, altered reuptake or reduced sensitivity of the postsynaptic receptor. Intracellular recordings from lumbosacral motor neurones in cats have shown that diethyl ether[15] depresses synaptic potentials, thus decreasing the amount of excitatory transmitter released while leaving the chemosensitivity of the postsynaptic membrane unchanged. We have shown recently that isoflurane reduced both synaptic (calcium-dependent) and non-synaptic (calcium-independent) potassium-stimulated release of glutamate from rat cerebral cortex,[16] without affecting the response on the postsynaptic membrane.[11] The effect on the presynaptic terminal may be caused by alteration in the uptake mechanism in addition to reduction in the release of transmitter.

To study further how isoflurane acts presynaptically, we have investigated the effect on neuronal reuptake mechanisms of glutamate using synaptosomes prepared from rat cerebral cortex.

## Materials and methods

### PREPARATION OF SYNAPTOSOMES

Synaptosomes were prepared, as described by McMahon and colleagues.[17] Briefly, Wistar rats, treated according to approved rules, were killed and the brain carefully removed. The cortex from each hemisphere was isolated and homogenized in 15 ml of sucrose 0.32 mol $litre^{-1}$ (1–4 °C) using a glass homogenizer with a Teflon pestle (clearance=0.25 mm). The homogenate was centrifuged at 3000×*g* for 3 min and the supernatant spun at 15 000 × *g* for 30 min. The pellet formed consisted of two layers. The superficial layer containing the majority of the synaptosomes[17] was resuspended selectively in 6 ml of sucrose 0.32 mol $litre^{-1}$, stored at 1–4 °C and used within 6 h from preparation. The pellet was diluted before use in HEPES-buffered medium (HBM) containing (mmol $litre^{-1}$): NaCl 117.5, KCl 3.75, $MgCl_2$ 1, $CaCl_2$ 1.3, $KH_2PO_4$ 1.25, $NaHCO_3$ 20, glucose 10, HEPES 20, NaOH 6 (pH 7.4). Fresh HBM was prepared daily.

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### L-GLUTAMATE UPTAKE

Synaptosomes (2–4 mg protein ml$^{-1}$) were incubated at 37 °C in a series of different concentrations of L-glutamate corresponding to the high- ($5.5\times10^{-6}$ to $2.5\times10^{-5}$ mol litre$^{-1}$) and low- ($1\times10^{-4}$ to $1\times10^{-3}$ mol litre$^{-1}$) affinity uptake systems, respectively.[18] A fixed concentration ($2.2\times10^{-9}$ mol litre$^{-1}$) of radiolabelled glutamate (46 Ci mmol$^{-1}$) (Amersham Laboratories, Buckinghamshire, UK) was added to each L-glutamate concentration. The chambers, each containing 1.5 ml of incubation medium, were sealed and saturated with 95% oxygen–5% carbon dioxide. Isoflurane 0.5, 1.5 or 3.0% (Abbot Laboratories Ltd., Kent, UK) was added using a vaporizer (Fortec, Ohmeda 5250 RGM, Englewood, USA) and the medium shaken gently every 30 s. Uptake was terminated at 4 min as the synaptosomes were placed on a Millipore filter (0.65 mm), washed in 5 ml of 0.9% NaCl (1–4 °C) and dissolved in 1 ml of 10% Triton X-100 (t-octylphenoxypolyethoxyethanol) (Sigma Chemical Co., St Louis, MO, USA) for 10 min. The suspension was then removed from the filter before scintillation fluid (Pico-Fluor 15, Packard, Groningen, The Netherlands) was added. The labelling was measured by counting disintegrations per minute in a β-scintillation counter (LKB Wallac, San Fransisco, CA, USA) with a counting efficiency of 25–30%. Protein content was measured using the method of Lowry and colleagues.[19]

In each setting, a control experiment and experiments using 0.5, 1.5 and 3.0% isoflurane were performed using one batch of synaptosomes from one brain. The number of experiments ($n=9$) thus reflects the number of rats used.

Results are presented as mean (SEM). Differences between the two groups were tested using the Wilcoxon signed rank sum test and for three or more groups with the Kruskal–Wallis test. Differences were considered significant when $P<0.05$.

## Results

In the first set of experiments, concentrations of L-glutamate were increased from $0.55\times10^{-5}$ to $2.5\times10^{-5}$ mol litre$^{-1}$ corresponding to the high-affinity uptake system with a reported $K_m$ value of $0.2\text{–}5.0\times10^{-5}$ mol litre$^{-1}$.[18,20] Uptake velocity for L-glutamate was measured in the control situation and under the influence of isoflurane in increasing concentrations (0.5, 1.5 and 3.0 %). The results are summarized in table 1. By plotting the mean values from table 1 in a double reciprocal plot (Lineweaver–Burk plot) as shown in figure 1, straight lines with regression coefficients ($r^2$) of 0.905 to 0.992 were drawn. *V*max and $K_m$ were calculated from the intercepts of the lines on the *Y* and *X* axis, respectively. The lowest concentration, 0.5% isoflurane, had no effect on uptake velocity as the control and 0.5% isoflurane plots were parallel. However, 1.5 and 3.0% isoflurane produced an increase in uptake velocity, as seen from the reduced steepness of the plot in figure 1. As all lines cross the *X* axis at approximately the same point, the high-affinity transporter to glutamate was presumably unaffected by isoflurane.

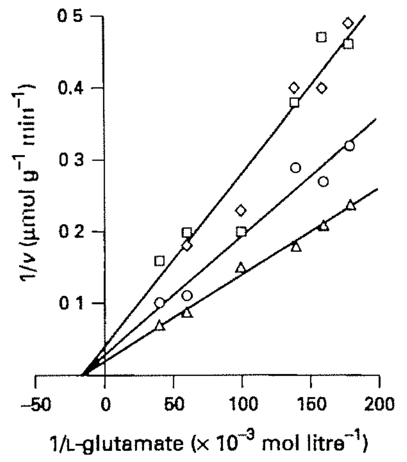

*Figure 1* Double-reciprocal plots of the effect of 0.5, 1.5 and 3.0% isoflurane on high- affinity glutamate transport in cortical synaptosomes. Regression lines are drawn. (Control (□), $r^2=0.905$; 0.5 % isoflurane (◇), $r^2=0.952$; 1.5% isoflurane (○), $r^2=0.958$; and 3.0% isoflurane (△), $r^2=0.992$.) Each point represents the mean of nine experiments. For variability, see table 2.

Calculated $K_m$ and *V*max values for the high-affinity uptake system are presented in table 2. *V*max in the control situation was 1.47 (1.25) μmol g$^{-1}$ min$^{-1}$, and there was no significant change in response to 0.5% isoflurane. However, 1.5 and 3.0% isoflurane increased *V*max to 1.97 (0.80) and 3.09 (1.52) μmol g$^{-1}$ min$^{-1}$, respectively ($P<0.05$), corresponding to 131% and 210% increases, on average. $K_m$ for the high-affinity transporter was 52.9 (50.2) μmol litre$^{-1}$. Isoflurane 0.5, 1.5 and 3.0% had no effect on $K_m$.

In the second set of experiments the effect of isoflurane on the low-affinity uptake system was investigated, using glutamate concentrations from $1\times10^{-4}$ to $1\times10^{-3}$ mol litre$^{-1}$. The double reciprocal plot in

*Table 1* Uptake velocity (μmol g$^{-1}$ min$^{-1}$) at different concentrations of L-glutamate in the high affinity range in the synaptosomal fraction from rat cerebral cortex. The effects of 0.5, 1.5 and 3.0 % isoflurane were tested (mean (SEM), $n=9$) * $P<0.05$

| | L-glutamate concentration ($\times10^{-5}$ mol litre$^{-1}$) | | | | | |
|---|---|---|---|---|---|---|
| Test group | 0.55 | 0.62 | 0.70 | 1.00 | 1.60 | 2.50 |
| Control | 0.55 (0.11) | 0.53 (0.09) | 0.65 (0.11) | 1.27 (0.18) | 1.25 (0.30) | 1.54 (0.60) |
| Isoflurane 0.5% | 0.52 (0.17) | 0.63 (0.23) | 0.71 (0.23) | 1.08 (0.36) | 1.37 (0.44) | 1.67 (0.49) |
| Isoflurane 1.5% | 0.79 (0.18)* | 0.93 (0.21)* | 0.85 (0.22)* | 1.27 (0.39) | 2.22 (0.62)* | 2.50 (0.91)* |
| Isoflurane 3.0% | 1.05 (0.11)* | 1.18 (0.10)* | 1.41 (0.12)* | 1.69 (0.22)* | 2.78 (0.37)* | 3.70 (0.63)* |

*Table 2* Estimated values for $K_m$ and $V_{max}$ for the high-affinity uptake system for glutamate in synaptosomes and the effects of 0.5, 1.5 and 3.0% isoflurane (mean (SEM), $n=9$).$^*P<0.05$

| Test group | $K_m$ ($\times 10^{-6}$ mol litre$^{-1}$) | $V_{max}$ (µmol g$^{-1}$ min$^{-1}$) |
|---|---|---|
| Control | 52.9 (50.2) | 1.47 (1.25) |
| Isoflurane 0.5% | 52.0 (21.0) | 1.45 (0.49) |
| Isoflurane 1.5% | 46.5 (19.1) | 1.97 (0.80)* |
| Isoflurane 3.0% | 61.7 (30.4) | 3.09 (1.52)* |

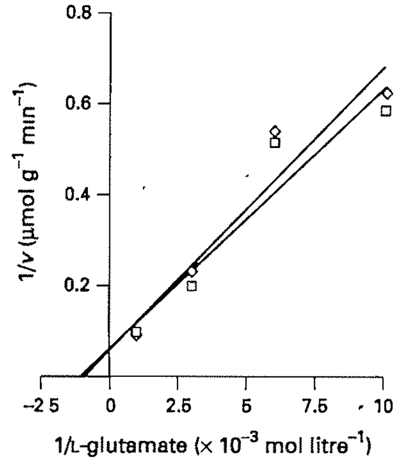

*Figure 2* Double-reciprocal plot of the effect of 1.5% isoflurane on the low-affinity uptake system for L-glutamate in synaptosomes. Regression lines are drawn. (Control (□, $r^2=0.909$; 1.5 % isoflurane (◇), $r^2=0.911$.) Each point represents the mean of seven experiments.

figure 2 describes a straight line with a regression coefficient of 0.904. As 0.5% isoflurane had no effect on the high-affinity uptake system, 1.5% isoflurane, which corresponds to approximately 1 MAC (minimal alveolar concentration), was tested. As is evident from figure 2, showing almost identical plots during control and isoflurane administration, 1.5% isoflurane had no effect on uptake velocity. *V*max for the low-affinity uptake system was calculated as 16.3 (11.9) µmol g$^{-1}$ min$^{-1}$, and 1.5% isoflurane had no effect on *V*max. The calculated $K_m$ value for the low-affinity uptake system was 1.0 (0.9) mmol litre$^{-1}$. $K_m$ was unaffected by 1.5% isoflurane.

## Discussion

Volatile anaesthetics seem to exert their effects in the central nervous system by affecting several different sites, including both excitatory and inhibitory pathways; for example isoflurane affects conduction in unmyelinated fibres, excitatory synaptic transmission, membrane properties of the postsynaptic neurone and inhibitory synaptic transmission.[9,11,12,21] However, the quantitatively most important effect is probably decreased excitatory synaptic transmission[10] which can be caused by decreased amount of transmitter released from the presynaptic terminal, more efficient reuptake from the synaptic cleft or reduced sensitivity of the postsynaptic membrane. This study showed an anaesthetic-induced increase in the uptake velocity of transmitter glutamate presynaptically. Taken together with the previously demonstrated decrease in transmitter release,[16] increased uptake further attenuates the excitatory synaptic transmission by faster termination of transmitter action.

The synaptosomal preparation used in this study is a mixture of pinched off nerve endings and to a large extent free from glial cells and cell debris.[22] The preparation consists of sealed plasma membrane vesicles with preserved release and uptake mechanisms.[23] Synaptosomes from rat cerebral cortex exhibit both high- and low-affinity uptake mechanisms for glutamate[18] and a high-affinity uptake system for γ-aminobutyric acid.[23] Because of well functioning secretory and uptake mechanisms, the method is regarded as well suited for studying neuronal release and uptake mechanisms of transmitters.[20]

Both neurones and glial cells have uptake systems important in terminating the effect of transmitter glutamate in the synaptic cleft.[20] We have demonstrated uptake systems both in low- and high-affinity areas with $K_m$ values of approximately 1 mmol litre$^{-1}$ and 50 µmol litre$^{-1}$, respectively. These are in agreement with previous reports of two different uptake systems in rat cortical synaptosomes, one in the low-affinity area with a $K_m$ value of approximately 1 mmol litre$^{-1}$ and the other in the high-affinity area with a $K_m$ value of 2–50 µmol litre$^{-1}$.[18,24] The physiological role of the low-affinity transporter is still unclear although it has been suggested that it prevents peak concentrations of extracellular glutamate.[25] The high-affinity uptake system, which is active in glial cells and in glutamatergic neurones, is important in terminating transmitter action.[25]

The mechanisms that regulate these transporter proteins are not fully understood. Four different glutamate transporters have recently been identified and cloned in human brain.[25,26] EAAT 1 (excitatory amino acid transporter) is localized only in the plasma membrane of glial cells, EAAT 2 in neurones and glial cells, EAAT 3 in neuronal plasma membranes[27] and EAAT 4 predominantly in cerebellum.[26] EAAT 1 is activated as protein kinase C (PKC) catalyses phosphorylation of the transporter protein.[28] In cultures of glial cells, stimulation of PKC activity with phorbol esters increases the high-affinity transport of L-glutamate seen as increased *V*max whereas $K_m$ is unaltered.[29] PKC stimulation also enhanced *V*max, but not $K_m$, of a cloned γ-aminobutyric acid transporter in *Xenopus* oocytes through translocation of the transporter from a cytoplasmic compartment to the plasma membrane.[30] Several volatile anaesthetics, including halothane and to some extent isoflurane, increase PKC-mediated phosphorylation of several rat brain cytoplasmic proteins in a calcium- and phospholipid-dependent manner.[31] One of these proteins, a major substrate for PKC, might have a regulatory role in neurotransmission.[31] As halothane and enflurane appear to inhibit PKC itself,[32] potential targets for anaesthetic action in intact neurones could be complex processes leading to release of intracellular calcium or production of diacylglycerol, which are both required for PKC activation. Furthermore, experimental observations have indicated that neurones may release factors that influence the activity of glutamate and GABA transporters in glial cells and thus suggest an alternative mechanism of action for anaesthetic agents.[33]

The potency of inhaled anaesthetics is described as the minimum alveolar concentration (MAC) of the gas producing surgical anaesthesia in 50% of subjects. The MAC value for isoflurane in middle-aged humans is 1.15% and for rats, 1.38%, and does not alter with increasing duration of anaesthesia. Concentrations exceeding 1 MAC are needed to depress the electroencephalogram (EEG) and at 2 MAC the EEG becomes isoelectric.[34] In this study, isoflurane was added to the incubation chambers in clinically relevant doses. The chambers were sealed in order to minimize gas leakage. If a small leakage should occur, however, the effect of the anaesthetic would occur at lower concentrations and the effect would thus be underestimated.

Isoflurane (0.5, 1.5 and 3.0%) increased high-affinity uptake of glutamate. A possible explanation could be an anaesthetic-induced increase in PKC activity catalysing phosphorylation and thereby activation of the transporter protein. This is in agreement with the previously mentioned activation of EAAT 1 in glial cells by PKC,[28 29 35] causing increased uptake velocity. Furthermore, this is in agreement with studies where halothane, and to some extent isoflurane, enhanced PKC activity on brain cytoplasmic proteins.[31] According to these observations, halothane and isoflurane can upregulate glutamate uptake through PKC-mediated activation of the transporter protein located on the presynaptic plasma membrane or induce translocation of transporters from the cytosol to the plasma membrane. This would subsequently reduce the amount of transmitter available for the postsynaptic membrane and restrict the time the transmitter is available in the synaptic cleft.

In this study, we have demonstrated that 1.5 and 3.0% isoflurane increased the uptake velocity in a dose-dependent manner. Isoflurane thus reduced excitatory synaptic transmission by reducing the amount of transmitter in the synaptic cleft.

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# Sevoflurane modulates both $GABA_A$ and $GABA_B$ receptors in area CA1 of rat hippocampus

K. Hirota and S. H. Roth

## Summary

It has been suggested that volatile anaesthetics enhance synaptic inhibition via γ-aminobutyric acid (GABA) in the central nervous system. We have examined the effects of sevoflurane on $GABA_A$ and $GABA_B$ receptors in rat hippocampus *in vitro.* Extracellular recordings were used to record field potentials in rat CA1 pyramidal neurones of transverse hippocampal slices, stimulated electrically via stratum radiatum input. Sevoflurane 0.4–5.0 vol% decreased the amplitudes of population spikes (PS) of CA1 neurones in a concentration-dependent (calculated $ED_{50}=6.31$ vol%) and reversible manner. The $GABA_A$ antagonist, bicuculline methiodide $5\times10^{-5}$ mol litre$^{-1}$, induced oscillations (multiple spikes) and blocked the inhibitory actions of sevoflurane in the initial component (up to 24.8 ms) of the oscillation. The latter portion of the oscillation (greater than 24.8 ms) was depressed by sevoflurane. The $GABA_B$ antagonist, phaclofen $5\times10^{-4}$ mol litre$^{-1}$ partially blocked the effects of sevoflurane on the latter portion of the bicuculline-induced oscillation. Sevoflurane 2.0 vol% significantly enhanced paired-pulse (PS2/PS1) facilitation (from 128.4% to 155.5% at an inter-stimulus interval of 37.9 ms); this enhancement was blocked by phaclofen. Stimulus–response relationships revealed that 2.0 vol% sevoflurane increased the intensity of threshold for PS generation to 109.8% of control. Both the $GABA_A$ agonist, muscimol $2\times10^{-5}$ mol litre$^{-1}$ and the $GABA_B$ agonist, (±)-baclofen $10^{-5}$ mol litre$^{-1}$, potentiated the effects of sevoflurane. Sevoflurane enhanced thresholds by 137.1% and 138.5% of control in the presence of muscimol and (±)-baclofen, respectively. The results demonstrate that sevoflurane at clinical concentrations activated both $GABA_A$- and $GABA_B$-mediated inhibitions in area CA1 of the hippocampus, and that sevoflurane and GABA agonists (muscimol and baclofen) acted on different domains on the $GABA_A$ and $GABA_B$ receptors, respectively. (*Br. J. Anaesth.* 1997; **78**: 60–65)

**Key words**
Anaesthetics volatile, sevoflurane. Brain, hippocampus. Receptors, amino acid. Rat.

Although the mechanism(s) by which volatile anaesthetics decrease neuronal excitability in the central nervous system are unknown, recent studies revealed that reduction in intrinsic excitability or synaptic response, or both, underlies the actions of general anaesthetics.[1–4]. Nicoll[5] suggested that general anaesthetics produce inhibitory actions because of γ-aminobutyric acid (GABA)-mediated synaptic inhibition.[6] The GABA analogue, THIP (4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol) was found to induce anaesthesia when administered systemically to rats.[7] Recent investigations have distinguished at least two types of GABA receptors: the bicuculline-sensitive receptor, termed $GABA_A$, which is a ligand-gated $Cl^-$ channel,[8] and the $K^+$ channel-modulating receptor, $GABA_B$, which is a G protein-coupled receptor.[9] It has been shown that halothane, enflurane and isoflurane modulate $GABA_A$ receptor-mediated $Cl^-$ currents.[10–14] Although possible involvement of $GABA_B$ receptors in the inhibitory actions of anaesthetics was suggested,[15 16] little is known of the effects of anaesthetics on $GABA_B$ receptors. Sevoflurane (fluoromethyl 2,2,2-trifluoro-1-[trifluoromethyl] ethyl ether) is a relatively new anaesthetic with rapid induction and recovery properties. It is reported that sevoflurane induces $Cl^-$ currents in CA1 neurones in rat hippocampus.[17] The main objectives of this study were to determine the involvement of $GABA_A$ and $GABA_B$ receptors in the actions of sevoflurane in area CA1 of rat hippocampus.

Previous studies have defined the selective agonist for the $GABA_A$ receptor, muscimol, the agonist for the $GABA_B$ receptor, baclofen, and the selective antagonist for the $GABA_A$ receptor, bicuculline.[8 9] Phaclofen, the phosphonic acid derivative of baclofen, was shown recently to be a selective $GABA_B$ antagonist.[18] These GABAergic agents are

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useful in determining the physiological significance and interactions of GABA receptors. In order to examine the modulation of hippocampal $GABA_A$ and $GABA_B$ receptors by sevoflurane, we have studied the effects of sevoflurane on the electrophysiological and pharmacological properties of the stratum radiatum input to CA1 pyramidal neurones of rat hippocampus *in vitro*. Extracellular recordings were used for the pharmacological investigations of synaptic activities.

## Materials and methods

### SOLUTIONS AND DRUGS

Artificial cerebrospinal fluid (ACSF) was made with 18 MΩ purity water (Baunstead Nanopure) and Analar grade chemicals. The composition was (mmol litre$^{-1}$): NaCl 124, KCl 5, $CaCl_2$ 2, $NaH_2PO_4$ 1.25, $MgSO_4$ 2, $NaHCO_3$ 26, glucose 10. ACSF (pH 7.3±0.1) was pre-cooled (8–10 °C) and saturated with a 95% oxygen–5% carbon dioxide gas mixture before use (pH 7.3–7.4).

Most of the chemicals used were obtained from BDH Inc. (Ontario, Canada) with the exception of muscimol, bicuculline methiodide (Sigma Chemical Co., MO, USA), (±)-baclofen and phaclofen (Research Biochemicals Inc., MA, USA). Sevoflurane was generously donated by Maruishi Pharmaceutical (Osaka, Japan).

### PREPARATION

The technique for preparation of rat hippocampal slices was identical to the method described previously by MacIver and Roth.[19] After obtaining approval from the Animal Care Committee of the University of Calgary, male Sprague–Dawley rats, weighing 100–200 g, were anaesthetized with ether and the brain removed rapidly and placed in pre-cooled (8–10 °C) ACSF. Transverse slices (350 μm) of hippocampus were cut using a tissue chopper (Stoelting, IL, USA). Slices were placed on a nylon mesh screen at the gas–liquid interface in a recording chamber. The temperature of the recording chamber was controlled at 35 °C with a pre-warmed (35 °C), perfusing (1.5 ml min$^{-1}$) ACSF and a pre-warmed and humidified 95% oxygen–5% carbon dioxide gas mixture (1.5 litre min$^{-1}$). Slices were incubated for 90 min without electrical stimulation.

### ELECTROPHYSIOLOGICAL TECHNIQUE

Bipolar nichrome stimulating electrodes were placed on the stratum radiatum to activate excitatory synaptic inputs to CA1 pyramidal neurones. A glass microelectrode was placed in the cell body regions of CA1 neurones for recording extracellular field potentials. The resistance of the microelectrode was 3–5 MΩ when filled with NaCl 2 mol litre$^{-1}$.

Stimuli were square-wave pulses generated by a Grass (MA, USA) S88 stimulator and a SIU5 stimulus isolation unit. A stimulus pulse of 0.05–0.5 ms duration was delivered at 0.1 Hz. The minimal stimulus intensity that elicited a maximal population spike (PS) amplitude ("maximal stimulus") was used except in experiments for stimulus–response (S-R) analysis. In some experiments, a paired-pulse stimulus was used to examine paired-pulse facilitation. In this case, the inter-stimulus interval was adjusted to elicit a maximal response, and the ratio of the first (PS1) and second population spike (PS2) amplitudes was determined (fig. 1). Field potentials were amplified with a Grass P15 amplifier (low- and high-frequency filters set at 1 Hz and 10 kHz), and digitally stored on VCR using a Neuro Data (NY, USA) DR-384 A/D converter for later analysis.

### DATA ANALYSIS

The amplitudes of PS and excitatory post-synaptic potential (EPSP) measurements were essentially the same as those described previously.[20] The duration of oscillation in the presence of bicuculline methiodide was determined as the distance between the first peak of PS and the last detectable peak. Results were collected in a group of four, averaged and stored as a single record. All preparations used in this study exhibited PS amplitudes of at least 5 mV and control variability less than 5% during the initial data acquisition period and after washout of sevoflurane.

Experiments were conducted on 54 hippocampal slices prepared from 49 rats. Results are expressed as mean (SEM), and comparisons were made using Student's *t* test. A probability of chance occurrence of less than 5% ($P<0.05$) was considered significant. Non-liner functions were fitted to the data using the SigmaPlot program (Jandel, CA, USA)

### DRUG ADMINISTRATION

Sevoflurane was applied as a vapour to the tissue chamber via the pre-warmed and humidified 95% oxygen–5% carbon dioxide gas stream above the slices, using a Tec 3 sevoflurane vaporizer (Ohmeda, West Yorkshire, UK). Concentrations, expressed as volume percentage (vol%), refer to dial settings on the vaporizer. The vaporizer had been calibrated previously with an anaesthetic gas analyser (Capnomac; Datax, Finland). Sevoflurane was applied for a minimum of 5 min to reach equilibrium, as the preliminary experiments demonstrated that the onset times for sevoflurane effects were less than 30 s and that maximum effects reached a plateau within 3 min (not shown) because of low solubility (a saline–gas coefficient of 0.370)[21] of the anaesthetic. Concentrations of sevoflurane in the perfusate of the recording chamber were measured using gas chromatography. The concentrations of anaesthetic in solution were found to be linearly correlated ($0.56 \times 10^{-3}$ mol litre$^{-1}$ per 1%) with the percentage in the gas phase up to 5.0%.

The GABAergic agents (muscimol, bicuculline methiodide, (±)-baclofen, phaclofen) were added to the ACSF at required concentrations just before each experiment. Slices were exposed for 15 min to the drug-containing ACSF, which was found to be sufficient time to produce stable effects.

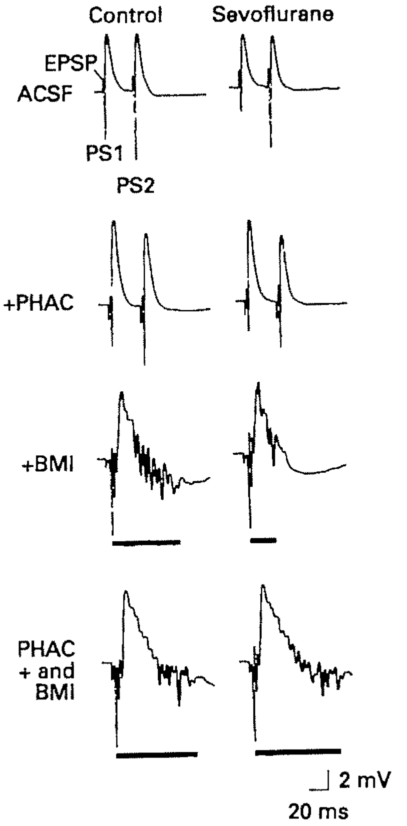

*Figure 1* Effects of 2.0 vol% sevoflurane on field potentials of CA1 neurones under normal artificial cerebrospinal fluid (ACSF) conditions, and after modulation of sevoflurane actions by phaclofen (+PHAC, $5\times10^{-4}$ mol litre$^{-1}$) and/or bicuculline methiodide (+BMI, $5\times10^{-5}$ mol litre$^{-1}$). Population spikes (PS1, PS2) (downward, negative wave) and excitatory postsynaptic potentials (EPSP) (positive, upward wave) were elicited by either paired-pulse stimuli (ACSF, +PHAC) or single stimuli (+BMI, +PHAC and BMI) at a fixed intensity and duration (0.1 Hz). Note that the later part of the oscillatory potentials (indicated by the straight lines in the lower two traces) were depressed by sevoflurane in the presence of bicuculline methiodide, whereas in the presence of both phaclofen and bicuculline methiodide the oscillation remained unchanged after administration of sevoflurane. Data in each series of records were obtained from separate preparations.

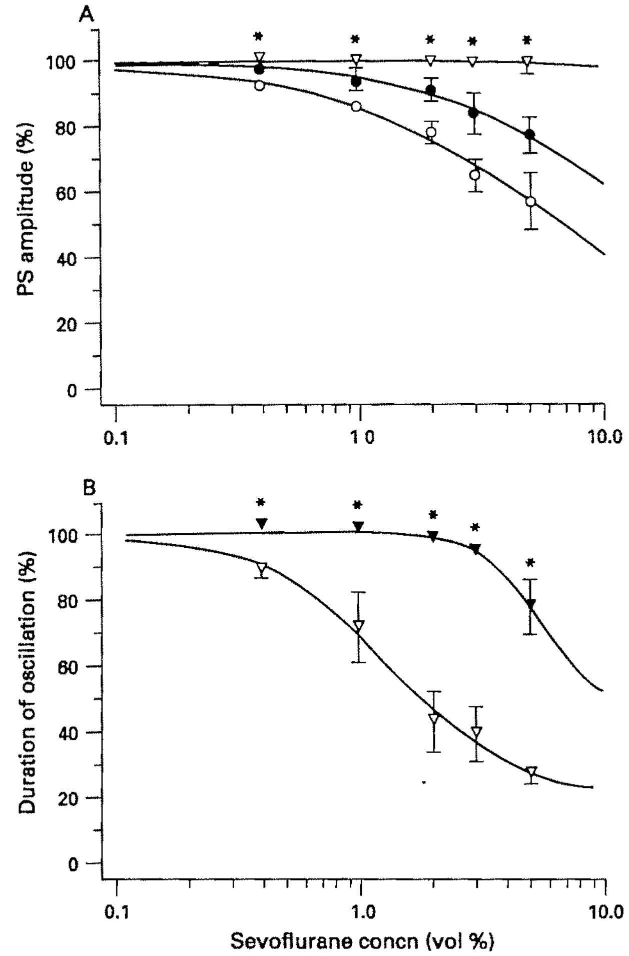

*Figure 2* Concentration–response relations of the amplitude of PS (A) and duration of oscillatory potentials (B) for sevoflurane in the absence (○) and presence of GABA antagonists, phaclofen (PHAC, $5\times10^{-4}$ mol litre$^{-1}$) (●), bicuculline methiodide (BMI, $5\times10^{-5}$ mol litre$^{-1}$) (▽) and PHAC and BMI (▼). Data points are percentage of control (mean, SEM). $^*P<0.05$ compared with data in the absence of GABA antagonists (A) or in the presence of BMI (B).

## Results

Figure 1 shows representative recordings of the effects of 2.0 vol% sevoflurane on field potentials of CA1 pyramidal neurones in the absence (top trace) and presence of GABA antagonists (lower three traces). Field potentials were elicited with either paired-pulse stimuli (upper two traces) or single stimuli (lower two traces) at 0.1 Hz.

Sevoflurane decreased the first (PS1) and second PS (PS2) amplitudes in a concentration-dependent and reversible manner (fig. 1, fig. 2A) without significant change in EPSP amplitudes. Using the SigmaPlot program, the data were fitted to an equation of the form:

$$\text{Amplitude (\%)} = \frac{k^n}{k^n + C^n} \times 100 \qquad (1)$$

where $k$=concentration producing 50% inhibition (ED$_{50}$), $C$=concentration of sevoflurane, and $n$=Hill's coefficient. The $k$ value (calculated ED$_{50}$) and Hill's coefficient obtained from data in figure 2A for sevoflurane were 6.3 vol% and 1.0, respectively.

### GABA ANTAGONISTS AND SEVOFLURANE

The GABA$_B$ antagonist phaclofen $5\times10^{-4}$ mol litre$^{-1}$ alone had no consistent effect on the shape of field potentials (fig. 1). Although phaclofen shifted the concentration–response curve for sevoflurane to the right ($k$=15.0 vol%), this change was not significant (fig. 2A). In contrast, the GABA$_A$ antagonist bicuculline methiodide $5\times10^{-5}$ mol litre$^{-1}$ caused long-lasting oscillatory potentials (92.5 (15.0) ms, $n$=4), and blocked the depressant actions of sevoflurane on the initial amplitude of the oscillatory PS (fig. 1). The amplitudes of PS1 (fig. 1, upper two traces) or the initial PS amplitudes (lower two traces) were used for data analysis.

Sevoflurane depressed the latter portion of bicuculline-induced oscillation (indicated by the straight lines in fig. 1). A concentration of 5.0 vol% decreased the duration of the oscillation to 25.9 (2.8) % of control (24.8 (6.7) ms, $n$=4) in the presence of bicuculline methiodide. However, phaclofen

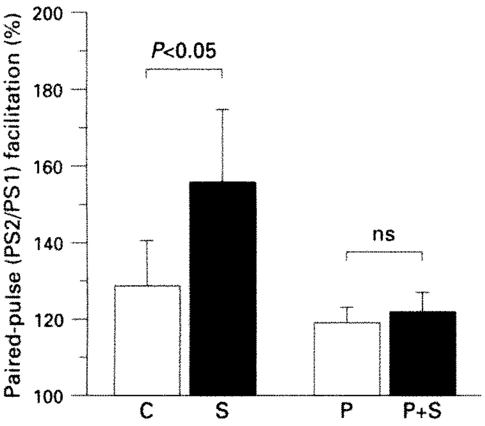

*Figure 3* Effects of sevoflurane and/or phaclofen on paired-pulse (PS2/PS1) facilitation. The inter-stimulus interval that elicits a maximal PS2 amplitude was used to determine the facilitation. Data are expressed as mean (SEM). C=Control (ACSF), $n=7$; S=2.0 vol% sevoflurane, $n=7$; P=phaclofen $5\times10^{-4}$ mol litre$^{-1}$, $n=3$; P+S=phaclofen and sevoflurane, $n=3$. Note that in the absence of phaclofen, sevoflurane significantly ($P<0.05$) enhanced paired-pulse facilitation, while in the presence of phaclofen, sevoflurane had no significant effect.

in combination with bicuculline methiodide partially blocked the decrease in duration induced by sevoflurane (fig. 2B). Data in figure 2B were fitted to a modification of equation (1):

$$\text{Amplitude }(\%)=\left(\frac{k^n(1-R)}{k^n+C^n}+R\right)\times 100 \qquad (2)$$

where $R$=sevoflurane-resistant portion (duration) of the oscillation; $k$ and $R$ values obtained from data in figure 2B were 1.3 vol% and 0.18, respectively, for bicuculline methiodide and 5.3 vol% and 0.44 for phaclofen with bicuculline methiodide.

Figure 3 shows the effects of sevoflurane and phaclofen on paired-pulse facilitation (PS1/PS2). A maximal PS2/PS1 facilitation was 128.4 (12.0) % ($n=7$) at an inter-stimulus interval of 37.9 (2.4) ms in the control state. Sevoflurane 2.0 vol% significantly enhanced the PS2/PS1 ratio to 155.5 (19.3) % ($n=7$). This change was caused mainly by marked depression of PS1, while PS2 was less affected. On the other hand, phaclofen $5\times10^{-4}$ mol litre$^{-1}$ decreased PS2/PS1 to 118.4 (3.9) % ($n=3$) at an inter-stimulus interval of 38.3 (2.0) ms and blocked the enhancement of PS2/PS1 by 2.0 vol% sevoflurane.

### GABA AGONISTS AND SEVOFLURANE

Figure 4 shows examples of the stimulus–response (S-R) relationships of PS in the absence and presence of GABA agonists. Stimulus intensity was varied to determine S-R relationships at a fixed stimulus duration and frequency. The data were fitted with non-linear functions generated with the SigmaPlot program; the maximal amplitudes of PS (*A*max) and thresholds for PS generation were calculated. Sevoflurane 2.0 vol% significantly enhanced the threshold (109.8 (3.8) % of control, $n=5$), however, *A*max remained unchanged (98.6 (1.3) % of control) in the absence of GABA agonists. The GABA agonists muscimol $2\times10^{-5}$ mol litre$^{-1}$ and (±)-baclofen $10^{-5}$ mol litre$^{-1}$ significantly increased the threshold and decreased *A*max.

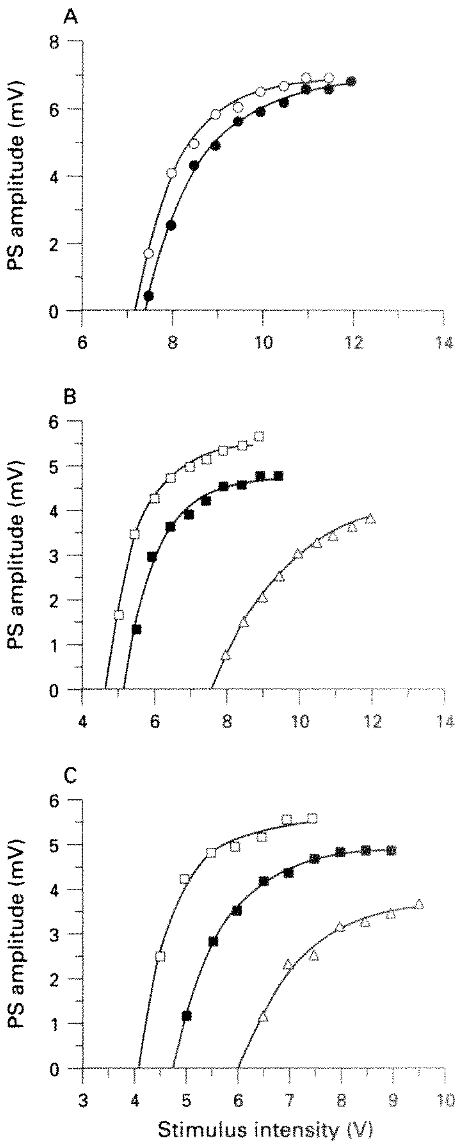

*Figure 4* Representatives of the stimulus–response (S-R) relations of PS amplitude in the presence of GABA agonists and/or 2.0 vol% sevoflurane. A: Effects of sevoflurane (control (○); 2.0 vol% sevoflurane (●)). B: Effects of $GABA_A$ agonist and/or sevoflurane (control (□); muscimol $2\times10^{-5}$ mol litre$^{-1}$ (■); muscimol and sevoflurane (△)). C: $GABA_B$ agonist and/or sevoflurane (control (□); (±)-baclofen ($10^{-5}$ mol litre$^{-1}$ (■)); baclofen and sevoflurane (△)). Data in each series of records were obtained from separate preparations.

Each GABA agonist potentiated the effects of sevoflurane (see fig. 4B, 4C). Sevoflurane 2.0 vol% increased the threshold (137.1 (6.2) % and 138.5 (11.2) %) and decreased *A*max (87.1 (2.8) % and 71.4 (5.9) %) in the presence of muscimol ($n=4$) and baclofen ($n=3$), respectively. These changes were significantly different from those observed in the absence of GABA agonists. Figure 5 shows a summary of the *synergistic* interactions between sevoflurane and the GABA agonists. The combination of 2.0 vol% sevoflurane and baclofen $10^{-5}$ mol litre$^{-1}$ increased the threshold by 56.8%, while the summation of the threshold changes produced by sevoflurane and baclofen independently was 23.5%.

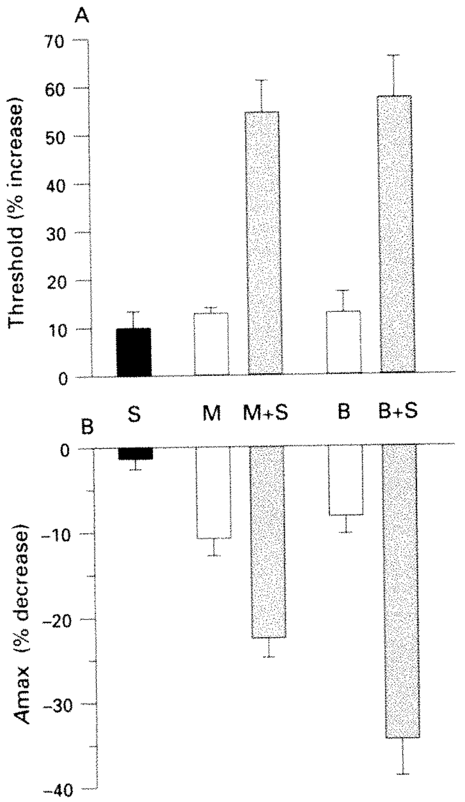

*Figure 5* Summary of the effects of sevoflurane and/or GABA agonists on threshold (A) and *A*max (B). Data (mean, SEM) are expressed as percentage increase (A) or percentage decrease (B) compared with control. S=2.0 vol% sevoflurane, $n=5$; M=muscimol $2\times10^{-5}$ mol litre$^{-1}$, $n=4$; M+S=muscimol and sevoflurane, $n=4$; B=baclofen $2\times10^{-5}$ mol litre$^{-1}$, $n=3$; B+S=baclofen and sevoflurane, $n=3$. All bar charts were significantly different ($P<0.05$) from control except for sevoflurane (2.0 vol%, S) in B.

## Discussion

The rat hippocampal slice preparation has served as a useful model system to study the mechanisms of action of general anaesthetics, and may be one of the major targets for anaesthetic action.[22] In addition, the anatomy, physiology and pharmacology have been well documented in numerous reports.

It had been demonstrated that the actions of sevoflurane on hippocampal PS may be caused by modulation of both GABA$_A$- and GABA$_B$-mediated inhibitions. Postsynaptic GABA$_A$ and GABA$_B$ receptors are thought to generate the fast inhibitory postsynaptic potential (f-IPSP) and the slow inhibitory postsynaptic potential (s-IPSP), respectively, in the central nervous system.[6 23] The f-IPSP and s-IPSP have been reported to have mean latencies of onset of ~3 ms and 29 (SEM 2) ms ($n=9$), respectively, in CA1 neurones of the rat hippocampus.[24] Bicuculline blocked the inhibitory actions of sevoflurane on the initial period of oscillation (figs 1, 2A). The duration of sevoflurane-resistant oscillation was up to 24.8 ms. These results indicate that sevoflurane activates GABA$_A$ responses to enhance f-IPSP.

Although GABA$_A$ antagonists have been reported to block the inhibitory actions of halothane, enflurane and isoflurane in rat hippocampal neurones,[13 25] less attention has been paid to the decrease in duration of bicuculline-induced oscillation by anaesthetics. The observed inhibition in the sevoflurane-sensitive component of the oscillation (>24.8 ms) is most likely a result of postsynaptic GABA$_B$-mediated inhibition, as the combination of phaclofen and bicuculline significantly blocked sevoflurane depression during the duration of the oscillation (figs 1, 2B).

Phaclofen, however, did not completely block the effects of sevoflurane on bicuculline-induced oscillation. Sevoflurane 5.0 vol% reduced the duration to 76.8% of control, and the calculated sevoflurane-sensitive component of the duration was 56% in the presence of phaclofen (fig. 2B). This suggests that other mechanism(s) in addition to GABAergic inhibition may be involved in the actions of sevoflurane. As it is reported that isoflurane inhibits voltage-gated Ca$^{2+}$ currents in rat hippocampal pyramidal neurones,[2] sevoflurane could affect ion channels of pyramidal neurones to reduce cellular excitability in area CA1. On the other hand, the results of effects of volatile anaesthetics on excitatory synaptic transmissions in the CNS have been contradictory. Although conventional extracellular and current-clamp experiments revealed that volatile anaesthetics have no consistent effect on excitatory synaptic transmissions in rat hippocampal CA1,[15 26] patch-clamp studies demonstrated that halothane and isoflurane depressed glutamate receptor-mediated excitatory postsynaptic currents in hippocampal neurones.[14] In our study, sevoflurane had no significant effects on EPSP amplitudes, suggesting that sevoflurane had minimal actions on excitatory synaptic transmissions.

Sevoflurane enhanced paired-pulse (PS2/PS1) facilitation and this enhancement was blocked in the presence of phaclofen (fig. 3). Although the mechanisms for the facilitation are not well understood, presynaptic GABA$_B$ receptors have been suggested to play a major role in the facilitation of CA1 neuronal activity of rat hippocampus. It is suggested that activation of GABA$_B$ autoreceptors after the first stimulation transiently depresses GABA release from presynaptic terminals.[23 27] Thus increased facilitation by sevoflurane may be attributed to activation of presynaptic GABA$_B$-mediated depression of GABA release.

Although volatile anaesthetics were reported to produce GABA$_A$-mediated inhibitions as a result of enhancement of GABA receptor–Cl$^-$ channel complex,[10–14] little is known of the effects of anaesthetics on hippocampal GABA$_B$ receptors. It has been reported that the GABA$_B$ agonist baclofen produces anaesthesia when administered systemically to mice,[16] and that prolongation of paired-pulse depression by halothane, enflurane and isoflurane in rat hippocampus *in vivo* might be caused by modulation of GABA$_B$ receptor-mediated inhibition.[15] Our results demonstrate that sevoflurane may enhance the effectiveness of the postsynaptic GABA$_B$ receptor and presynaptic GABA$_B$ autoreceptor.

If the mechanisms for GABA receptor activation by sevoflurane are the same as those for GABA agonists, the combination of sevoflurane and GABA agonists would be expected to induce additive or less than additive effects. Our results, however, demonstrated that administration of sevoflurane in the presence of muscimol or baclofen evoked a synergistic response (figs 4, 5). Hence different mechanisms for sevoflurane and GABA agonists may be involved in the activation of GABA receptors. Our results are in accordance with the proposed hypothesis that the binding site for general anaesthetic molecules is located in the GABA receptor complex, and that this site is different from the GABA recognition site.[28 29]

In summary, we have shown that sevoflurane activates postsynaptic $GABA_A$ receptors, and post- and presynaptic $GABA_B$ receptors in CA1 pyramidal neurones of rat hippocampus *in vitro*, and that sevoflurane and GABA agonists (muscimol, baclofen) acted on different domains of the GABA receptor complex. $GABA_A$- and $GABA_B$-mediated inhibition may represent an important role for sevoflurane in producing general anaesthetics.

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# Volatile anaesthetic effects on calcium conductance of planar lipid bilayers formed with synthetic lipids or extracted lipids from sarcoplasmic reticulum

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## Summary

Volatile anaesthetics are known to increase leakage of calcium from the light fraction of skeletal sarcoplasmic reticulum (L-SR) which has no calcium release channels. To explore the role of the lipid environment, we have examined the effect of volatile anaesthetics on calcium conductance ($g_{Ca}$) of lipid membranes. Planar lipid bilayers were formed with a mixture of synthetic phospholipids and cholesterol, resembling the composition of SR membranes, or with lipids extracted from skeletal L-SR. $g_{Ca}$ was estimated by calculating the calcium transference number ($t_{Ca}$) using diffusion potential measurements. Membranes formed with L-SR-extracted lipids had a higher $g_{Ca}$ than membranes formed with synthetic lipids. Volatile anaesthetics increased total conductance and $g_{Ca}$ in a dose-dependent manner, but did not affect $t_{Ca}$ or membrane specific capacitance. In membranes formed with L-SR-extracted lipids, isoflurane induced the largest increase in $g_{Ca}$ (1260 (SEM 304) % increase, $n$=4, 0.94 mmol litre$^{-1}$), followed by enflurane (264 (75) %, $n$=5, 1.88 mmol litre$^{-1}$) and halothane (53 (33) %, $n$=5; 1.54 mmol litre$^{-1}$). In membranes formed with synthetic lipids, volatile anaesthetic-induced increases in $g_{Ca}$ followed the same trend but were larger. Volatile anaesthetics increased $g_{Ca}$ without changing the ionic selectivity of membranes. However, the magnitude of the increase in $g_{Ca}$ in the presence of volatile anaesthetics cannot account for the previously observed calcium leakage from L-SR vesicles. Therefore, the volatile anaesthetic-induced increase in calcium leakage in L-SR vesicles must be mediated via other pathways involving membrane proteins. (*Br. J. Anaesth.* 1997; **78**: 66–74)

**Key words**
Ions, calcium. Ions, ion channels. Anaesthetics volatile. Membrane, lipid bilayer. Theories of anaesthetic action, lipid bilayer.

The volatile anaesthetics halothane, enflurane and isoflurane alter calcium homeostasis in many cells. Volatile anaesthetics alter cellular $Ca^{2+}$ in part by acting on the sarcoplasmic reticulum (SR). They have been shown to increase the rates of $Ca^{2+}$ release[1–5] and of $Ca^{2+}$ uptake[5 6] from the SR. The former effect results from a volatile anaesthetic-induced increase in the open probability of calcium release channels,[7] increase in the rate of ATP breakdown[1 5] and decrease in SR calcium pump activity.[8–10] The increase in the rate of $Ca^{2+}$ uptake results from an increase in SR calcium pump activity when volatile anaesthetics are present at low concentrations.[1 5 9] Volatile anaesthetics also increase $Ca^{2+}$ leakage in vesicles isolated from the light SR (L-SR), which lacks calcium release channels.[1] The latter effect might be caused by a volatile anaesthetic action on the SR lipid membrane, enhancement of leakage pathways through membrane proteins or action on the interface between membrane lipids and proteins.

We have investigated one of these possibilities, the effect of volatile anaesthetics on $Ca^{2+}$ permeability of SR lipid membranes. It has been shown previously in liposomes that halothane increases membrane permeability to monovalent cations ($K^+$, $Rb^+$) and protons.[11 12] Therefore, it is expected that volatile anaesthetics should also increase $Ca^{2+}$ permeability of lipid membranes. Using the planar lipid bilayer system, we have investigated to what extent volatile anaesthetics affected $Ca^{2+}$ permeability of lipid membranes formed with either synthetic or L-SR-extracted lipids. We found that at the concentrations studied, volatile anaesthetics did not affect membrane-specific capacitance or ionic selectivity but significantly increased overall membrane ionic permeability (up to 10-fold). However, the magnitude of this increase was too small to account for the previously observed volatile anaesthetic-induced increase in $Ca^{2+}$ leakage in isolated L-SR-vesicles.

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## Materials and methods

### LIPID COMPOSITION OF PLANAR LIPID BILAYERS

Two mixtures of synthetic lipids were used: one consisted of a mixture of the neutral lipids palmitoyl-linoleoyl phosphatidylcholine, palmitoyl-arachidonyl phosphatidylethanolamine and cholesterol at a molar fraction of 7.5:2.5:1. This ratio was chosen to mimic the reported lipid composition of muscle SR.[13 14] The second lipid mixture contained the same components as the first mixture and 10% phosphatidylinositol. The latter was selected because SR lipids contain negatively charged phospholipids (approximately 10%), the main one being phosphatidylinositol.[13 15] Lipids were purchased from Avanti Polar Lipids, Inc. The lipid mixture was dissolved in decane (5% w/v) to form planar–lipid bilayers, as described previously.[16]

L-SR vesicles were isolated from rabbit skeletal muscle,[1] resuspended with distilled water (approximately 8.3 mg protein/ml) and lyophilized. Lipids were extracted[17 18] and stored in chloroform/methanol (2/1) at −20°C. The phospholipid content was measured by a phosphorus assay.[19] The phosphorus content of lipid extract was 0.72 mm/mg SR protein. To form planar–lipid bilayers, the chloroform–methanol was evaporated and the lipids dissolved in decane (5% w/v). Decane was used as it has been shown that it has little effect on blocking nerve impulses and on membrane thickness.[20] The data shown were obtained using a single preparation of L-SR-extracted lipids. Other L-SR-extracted lipid preparations were used in pilot experiments.

The bilayer chamber contained two compartments (1.24 ml capacity) separated by a partition with a hole (0.2–1.0 mm diameter) where lipid bilayers were formed. The front and back compartments are referred to as *cis* and *trans*, respectively. Silver–silver chloride electrodes were placed in each compartment; the reference electrode was placed in the *trans* compartment. The compartments contained 1 ml of a given solution. Salt bridges were not used during the experiments with $CaCl_2$ solutions. When asymmetrical $CaCl_2$ solutions were used, the applied potential was corrected for the estimated electrode–liquid potential differences.[21] For the experiments using sucrose solution, KCl 3 mol litre$^{-1}$ salt bridges were used to stabilize the electrode offset.

### MEMBRANE CONDUCTANCE AND CAPACITANCE MEASUREMENTS

Total membrane conductance ($g_m$), that is conductance caused by all ion species present in the solution, was measured using symmetrical solutions of $CaCl_2$ 200 mmol litre$^{-1}$. Slope conductances were obtained from linear fits of the current–voltage relationships constructed by applying 25-mV voltage steps between +50 and −50 mV. Holding potentials were maintained for 1–2 min to eliminate the contribution of slow capacitive currents. Membrane capacitances were calculated by measuring capacitive currents after applying 1-mV triangular voltage steps at a frequency of 100 Hz. Membranes were seen with a 120-times magnification and their diameter, limited by a visible torus, was measured with a graduated grid (2.5 μm/division). Membrane surface area was calculated assuming that the shape of the membrane was an ellipse. All solutions contained HEPES 2 mmol litre$^{-1}$ at pH 6.0. Free acid HEPES of the best grade was used (Sigma Chemical Co., St Louis, MO, USA). We used a pH value of 6.0 to reduce proton–hydroxide conductance ($g_{H^+OH^-}$).[22]

Total membrane conductance ($g_m$) was measured using symmetrical solutions of $CaCl_2$ 0.2 mol litre$^{-1}$. In all cases it was assumed that the conductance caused by the anion form of HEPES was negligible.

### DIFFUSION POTENTIAL MEASUREMENTS AND ESTIMATIONS OF TRANSFERENCE NUMBER

To obtain the relative membrane ionic selectivity for calcium over chloride, we estimated the transference number of $Ca^{2+}$ ($t_{Ca}$) by measuring diffusion potentials as described previously.[22–24] The zero current level was first measured in symmetrical $CaCl_2$ 20 mmol litre$^{-1}$ by applying 0 mV. The concentration of $CaCl_2$ was then increased in the *cis* compartment in a stepwise manner to 60, 120 and 200 mmol litre$^{-1}$ by addition of $CaCl_2$ 1 mol litre$^{-1}$, and the potential required to re-establish the zero current level (diffusion potential) was determined by interpolation of the current measurements obtained at 2–3 different membrane potentials. Changes in diffusion potential were obtained at every dose of volatile anaesthetic for membranes formed with synthetic lipids, and at the median and high doses of volatile anaesthetics for membranes formed with L-SR-extracted lipids. The $t_{Ca}$ was calculated by equation (1), assuming that only $Ca^{2+}$ and $Cl^-$ ions carried the ionic current (see Appendix for derivation).

$$V_d = (1 - 1.5t_{Ca}) \times (RT/F) \times \ln (a_{cis}/a_{trans}) \quad (1)$$

where $V_d$=measured diffusion potential, $R$=gas constant, $T$=temperature in Kelvin, $F$=Faraday constant, $a_{cis}$=mean salt activity of *cis* chamber and $a_{trans}$=mean salt activity in *trans* chamber. Values for mean salt activity were interpolated from previously reported values.[25] In most cases, $t_{Ca}$ values were estimated using a 10-fold concentration gradient. In some cases, $t_{Ca}$ values were obtained using a six-fold concentration gradient.

### ADDITION OF VOLATILE ANAESTHETICS AND MEASUREMENT OF VOLATILE ANAESTHETIC CONCENTRATIONS

Stock solutions of saturated volatile anaesthetics were prepared[1] in either sucrose 0.6 mol litre$^{-1}$, $CaCl_2$ 20 mmol litre$^{-1}$ or $CaCl_2$ 200 mmol litre$^{-1}$. A small volume (20–100 μl) of the bath solution was first removed and then replaced by an equal volume of the bath solution saturated with a volatile anaesthetic. After each addition of volatile anaesthetic (to both compartments), the chamber compartments were covered with glass coverslips and solutions stirred continuously for 1 min. The volatile anaesthetic concentration in the stock and chamber solutions was determined by gas chromatography.[26]

*Table 1* Estimated values for the hypothetical MAC at 25 °C (H-MAC) and the corresponding hypothetical aqueous concentration at 25 °C (H-$EC_{50}$). H-MAC and H-$EC_{50}$ were obtained using equations (2) and (3) as described under materials and methods

| | MAC(30) (37 °C) | H-MAC (25 °C) | H-$EC_{50}$ (25 °C) |
|---|---|---|---|
| Isoflurane | 2 1% | 0 93% | 0.47 |
| Halothane | 1.4% | 0.62% | 0.32 |
| Enflurane | 2.9% | 1.29% | 0.66 |

As experiments were performed at room temperature (approximately 25 °C), the magnitude of volatile anaesthetic effects at 37 °C are uncertain. To attempt a comparison of the relative potency of the volatile anaesthetics, we also present the volatile anaesthetic concentration as the ratio of the hypothetical aqueous concentration (H-$EC_{50}$) corresponding to the hypothetical MAC at 25 °C. This was done in the following way. First, we estimated the hypothetical MAC value at 25 °C (H-MAC (25 °C)) using equation (2) derived from Franks and Lieb.[27]

$$\text{H-MAC } (Tc)/\text{MAC } (37\,°\text{C}) = \exp\left(-20.2\,(37-Tc)/(273.15+Tc)\right) \qquad (2)$$

Then, using H-MAC (25 °C) we estimated the corresponding hypothetical aqueous concentrations (mmol litre$^{-1}$) (H-$EC_{50}$) using equation (3).[27]

$$\text{H-}EC_{50}\ (\text{mmol litre}^{-1}) = 0.44614\,\alpha\text{MAC } (\%) \qquad (3)$$

where $\alpha$=Bunsen water/gas partition coefficient. At 25 °C, $\alpha$ values are similar for halothane (1.20) and isoflurane (1.08),[28] but there is no reported value for enflurane. As the three volatile anaesthetics have similar $\alpha$ values at 37 °C,[28 29] we assumed that this also held true at 25 °C, and used a mean $\alpha$ value of 1.14 for all three volatile anaesthetics. We used MAC values from rabbits[30] as the extracted SR lipids were from rabbit skeletal muscle (table 1).

*Table 2* Membrane areas and specific capacitance values for membranes formed with synthetic neutral lipids (Synthetic) and with L-SR-extracted lipids (L-SR) in the absence and presence of volatile anaesthetic (mean (SEM)). (In all cases the partition hole was 0.2 mm in diameter)

| Anaesthetic (mmol litre$^{-1}$) | Membrane area ((cm$^2$)×10$^{-4}$) | Membrane capacitance (μF cm$^{-2}$) | *n* |
|---|---|---|---|
| Synthetic | | | |
| Control | 1.76 (0.12) | 0.61 (0.11) | 6 |
| Isoflurane 0.40 | 1.91 (0.18) | 0.66 (0.09) | 6 |
| Isoflurane 0.72 | 1.96 (0.22) | 0.69 (0.51) | 6 |
| Isoflurane 0.94 | 2.02 (0.20) | 0.70 (0.39) | 6 |
| Control | 1.79 (0.17) | 0.61 (0.15) | 4 |
| Halothane 0.32 | 1.74 (0.17) | 0.62 (0.16) | 4 |
| Halothane 0.78 | 1.81 (0.18) | 0 67 (0.15) | 4 |
| Halothane 1.54 | 1.76 (0 16) | 0.72 (0.14) | 4 |
| Control | 1.64 (0.20) | 0.73 (0.07) | 5 |
| Enflurane 0.80 | 1.52 (0.23) | 0.72 (0.78) | 5 |
| Enflurane 1.32 | 1.56 (0.24) | 0.69 (0.79) | 5 |
| Enflurane 1.88 | 1.52 (0.22) | 0.68 (0.80) | 5 |
| L-SR | | | |
| Control | 0.93 (0.35) | 1.11 (0.18) | 6 |
| Isoflurane 0.40 | 0.88 (0.32) | 1.19 (0.27) | 6 |
| Isoflurane 0.72 | 0.84 (0.34) | 1.23 (0.20) | 6 |
| Isoflurane 0.94 | 0.90 (0.36) | 1.30 (0.20) | 6 |
| Control | 1.06 (0.23) | 0.75 (0.08) | 6 |
| Halothane 0.32 | 0.87 (0.18) | 0.77 (0.07) | 6 |
| Halothane 0.78 | 0.99 (0.26) | 0.79 (0.07) | 6 |
| Halothane 1.54 | 0.97 (0.20) | 0.77 (0.13) | 6 |
| Control | 0.86 (0.17) | 0.99 (0.24) | 4 |
| Enflurane 0.80 | 0.94 (0.18) | 0.70 (0.06) | 4 |
| Enflurane 1 32 | 0.66 (0.22) | 0.62 (0.07) | 4 |
| Enflurane 1.88 | 0.90 (0.23) | 0.89 (0.25) | 4 |

### STATISTICS

Results are presented as mean (SEM). Differences between values obtained from synthetic and L-SR-extracted lipids in the absence of anaesthetic were analysed using the Mann–Whitney rank sum test. Differences between control and anaesthetics values were analysed by Friedman's test followed by the non-parametric Dunnett's test based on rank sum as *post hoc* analysis. In all cases, $P<0.05$ was considered significant.

## Results

### SPECIFIC CAPACITANCE

Under control conditions, membranes formed with L-SR-extracted lipids were smaller and had higher specific capacitance values than membranes formed with synthetic lipids (tables 2, 3). Such differences could reflect the presence of negatively charged phospholipids, as membranes formed with synthetic lipids containing negatively charged phospholipids had membrane areas and specific capacitance values resembling those of membranes formed with L-SR-extracted lipids (table 3).

*Table 3* Electrical properties and calculated calcium permeability in membranes formed with synthetic and L-SR-extracted lipids (mean (SEM)). $n$=number of membranes. For synthetic neutral lipids $n$=15 except for $t_{Ca}$ and $g_{msucr}$, $n$=4 For L-SR-extracted lipids, $n$=16 except for $t_{Ca}$, $n$=3. For synthetic neutral+charged lipids, $n$=6. $A_m$=membrane area, $C_m$=specific membrane capacitance; $g_m$=total specific membrane conductance in $CaCl_2$; $t_{Ca}$=transference number for calcium; $g_{Ca}$=specific calcium conductance; $P_{Ca}$=calcium permeability; $g_{msucr}$=total specific membrane conductance in sucrose. *Significantly different from synthetic neutral lipid, $P<0.05$. **Significantly different from synthetic neutral lipid, $P<0.01$

| | Synthetic neutral lipids | L-SR-extracted lipids | Synthetic neutral +charged lipids |
|---|---|---|---|
| $A_m$(cm$^2$) | 1.73 (0.01)×10$^{-4}$ | 0.96 (0.16)×10$^{-4}$** | 0.71 (0.13)×10$^{-4}$* |
| $C_m$ (μF cm$^{-2}$) | 0.65 (0.06) | 0.88 (0.07)** | 1.05 (0.04)* |
| $g_m$ (S cm$^{-2}$) | 1.31 (0.17)×10$^{-8}$ | 3 96 (0.58)×10$^{-8}$** | 2.43 (0.32)×10$^{-8}$* |
| $t_{Ca}$ | 0.40 (0.02) | 0.56 (0.01)* | |
| $g_{Ca}$ (S cm$^{-2}$) | 0.52 (0.07)×10$^{-8}$ | 2.22 (0.32)×10$^{-8}$** | |
| $P_{Ca}$ (cm s$^{-1}$) | 1.61 (0.22)×10$^{-12}$ | 6.87 (0.99)×10$^{-12}$** | |
| $g_{msucr}$(S cm$^{-2}$) | 1.34 (0.01)×10$^{-8}$ | | |

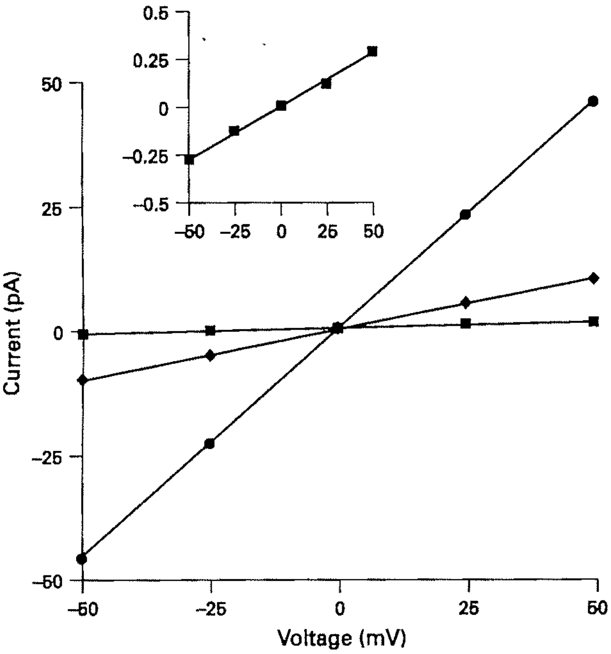

*Figure 1* Current–voltage relationships of membranes formed with synthetic neutral lipids measured in the presence of $CaCl_2$ 200 mmol litre$^{-1}$ before and after addition of isoflurane. Each point represents the mean value from 3–5 membranes, in the absence (■) and presence of isoflurane 0.72 mmol litre$^{-1}$ (◆) and 0.92 mmol litre$^{-1}$ (●). Inset shows the current–voltage relationship for control at an expanded scale. The lines represent linear regression fits for each condition and have the following values: $y=0.005x-0.001$, $r^2=0.998$ for control; $y=0.187x-0.113$, $r^2=1.000$ for isoflurane 0.72 mmol litre$^{-1}$ and $y=0.901x-0.333$, $r^2=1.000$ for isoflurane 0.92 mmol litre$^{-1}$

The area and specific capacitance of membranes formed with synthetic or L-SR-extracted lipids were not changed significantly by isoflurane, halothane or enflurane (table 2). Therefore, within the concentration range studied, these volatile anaesthetics did not affect membrane dimensions (area and specific capacitance).

## TOTAL MEMBRANE CONDUCTANCE IN $CACL_2$

In the absence and presence of anaesthetic, current–voltage relationships were linear from +50 to −50 mV (fig. 1). $g_m$ was significantly higher in membranes formed with L-SR-extracted lipids than in membranes formed with synthetic neutral lipids (table 3). When phosphatidylinositol was added to the mixture of lipids, $g_m$ values were between those for membranes formed with synthetic neutral lipids and L-SR-extracted lipids (table 3). All three volatile anaesthetics increased $g_m$ in a dose-dependent manner; in all cases, the dose–response curves were linear with the log of $g_m$ (fig. 2). The strongest effect was shown by isoflurane and the weakest effect by halothane; the effect of enflurane was intermediate. The magnitude of the volatile anaesthetic-induced increase in $g_m$ was lower in membranes formed with L-SR-extracted lipids than in membranes formed with synthetic lipids.

## TRANSFERENCE NUMBER FOR CALCIUM

In order to determine the ionic selectivity of membrane

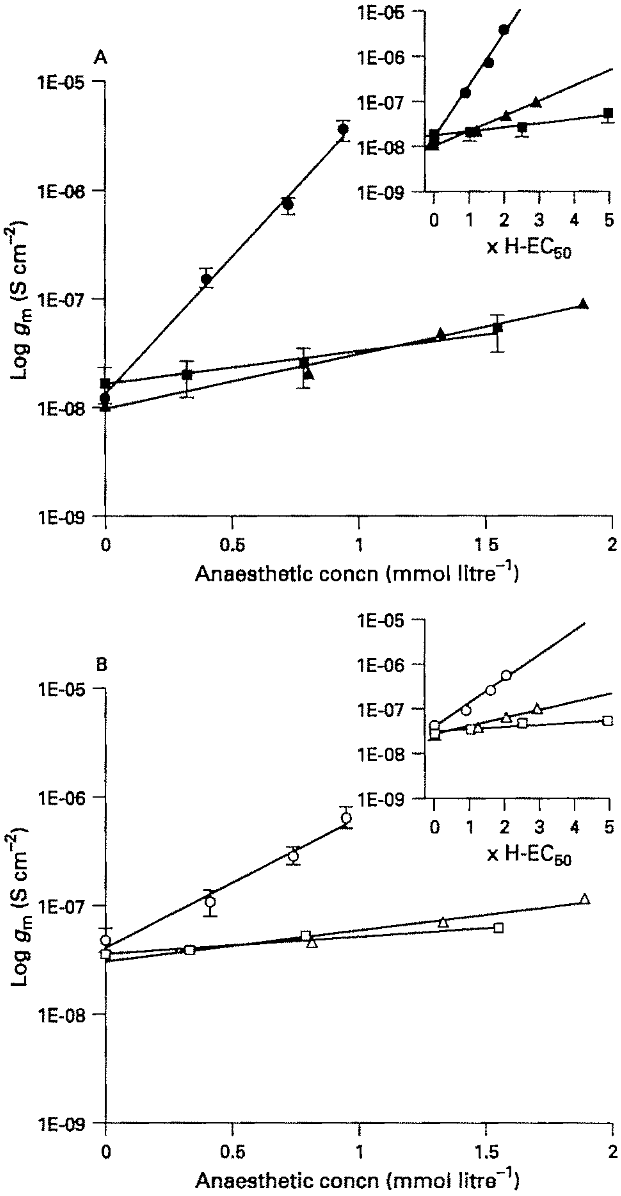

*Figure 2* Effects of volatile anesthetics on total specific membrane conductance. Total specific membrane conductance ($g_m$) measurements were performed in symmetrical solutions of $CaCl_2$ 200 mmol litre$^{-1}$ in membranes formed with synthetic neutral lipids (A) and with L-SR-extracted lipids (B). The anaesthetic concentration in the aqueous solution is given in mmol litre$^{-1}$ and as the ratio of the hypothetical-aqueous concentration (H-$EC_{50}$) corresponding to the hypothetical MAC at 25°C (insets). The data were fitted to a single exponential function. The fits of the data collected in membranes formed with synthetic lipids gave the following values: $y=1.31\times10^{-8}\times10^{2.53\times X}$ ($r^2=0.99$), $y=1.60\times10^{-8}\times10^{0.31\times X}$ ($r^2=0.97$), and $y=0.98\times10^{-8}\times10^{0.50\times X}$ ($r^2=0.99$) for isoflurane (●) (six membranes), halothane (■) (four membranes) and enflurane (▲) (five membranes), respectively for log $g_m$ *vs* mmol litre$^{-1}$; and $y=1.31\times10^{-8}\times10^{1.19\times X}$ ($r^2=0.99$), $y=1.60\times10^{-8}\times10^{0.10\times X}$ ($r^2=0.97$) and $y=0.98\times10^{-8}\times10^{0.33\times X}$ ($r^2=0.99$) for isoflurane, halothane and enflurane, respectively for log $g_m$ *vs* xH-$EC_{50}$. The fits of the data collected in membranes formed with L-SR-extracted lipids gave the following values: $y=4.27\times10^{-8}\times10^{1.20\times X}$ ($r^2=0.99$), $y=3.56\times10^{-8}\times10^{0.17\times X}$ ($r^2=0.92$) and $y=3.17\times10^{-8}\times10^{0.28\times X}$ ($r^2=0.96$) for isoflurane (○) (six membranes), halothane (□) (six membranes) and enflurane (△) (four membranes), respectively, for log $g_m$ *vs* mmol litre$^{-1}$; and $y=4.27\times10^{-8}\times10^{0.56\times X}$ ($r^2=0.98$), $y=3.56\times10^{-8}\times10^{0.06\times X}$ ($r^2=0.92$) and $y=3.17\times10^{-8}\times10^{0.19\times X}$ ($r^2=0.96$) for isoflurane, halothane and enflurane, respectively for log $g_m$ *vs* xH-$EC_{50}$. The data points represent mean (SEM). The observed increases in $g_m$ were significant at all doses of volatile anaesthetic except that observed at the lowest dose of halothane in membranes formed with L-SR-extracted lipids.

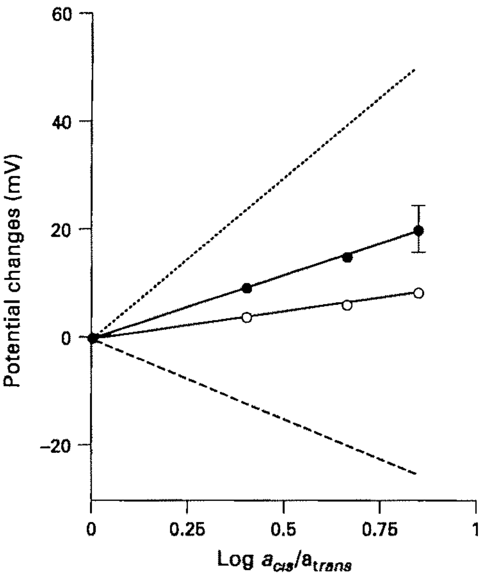

*Figure 3* Diffusion potentials in various $CaCl_2$ concentration gradients of membranes formed with synthetic neutral and L-SR-extracted lipids. Diffusion potentials were measured as described under materials and methods and plotted against the logarithmic ratio of salt activity of *cis* to *trans* solution. ●=Mean of four membranes formed with synthetic lipids and ○=mean of three membranes formed with L-SR-extracted lipids. The regression line gave the following values: $y=23.28\times x-0.008$ ($r^2=0.998$) and $y=9.72\times x-0.04$ ($r^2=0.999$) for synthetic and L-SR- extracted lipids, respectively. The Nerst potential values for $Cl^-$ (dotted line) and $Ca^{2+}$ (broken line) are indicated Data points are mean (SEM). Lipid membranes were initially formed in symmetrical $CaCl_2$ 20 mmol $litre^{-1}$, then the concentration of $CaCl_2$ in the *cis* compartment was increased. Membrane potential ($V_m$) was obtained by adding to the command potential ($V_{cmd}$) estimated electrode–liquid potential differences ($E_R$) (−20.1, −32.2 and −40.1 mV for 60/20, 120/20 and 200/20 mmol $litre^{-1}$ of $CaCl_2$, *cis/trans*) (e.g. in $CaCl_2$ 60/20, gradient for $V_{cmd}=+50$ mV, $V_m=+50+(-20)=+30$ mV). $E_R$ results from the electrodes being exposed to different concentrations of $Cl^-$ and was calculated using the following expression. $E_R=-2.303(RT/F)\log(aCl^-_{cis}/aCl^-_{trans})$ where $aCl^-$=activity of $Cl^-$ in either the *cis* or *trans* compartments.[21 25]

*Table 4* Calcium transference number ($t_{Ca}$) in the absence and presence of volatile anaesthetic (mean (SEM)). $n=3$ membranes in all cases except for control with synthetic lipids where $n=4$ membranes

| Anaesthetic (mmol $litre^{-1}$) | Synthetic lipids $t_{Ca}$ | L-SR-extracted lipids $t_{Ca}$ |
|---|---|---|
| Control | 0.40 (0.02) | 0.56 (0.01) |
| Isoflurane 0.40 | 0.45 (0.03) | |
| Isoflurane 0.72 | 0 37 (0.02) | 0.56 (0.01) |
| Isoflurane 0.94 | 0.40 (0 03) | |
| Halothane 0.32 | 0.47 (0.08) | |
| Halothane 0 78 | 0.45 (0.02) | 0.48 (0.08) |
| Halothane 1.54 | 0.52 (0.05) | |
| Enflurane 0.80 | 0.51 (0.05) | |
| Enflurane 1.32 | 0.49 (0.04) | 0.60 (0.01) |
| Enflurane 1.88 | 0.40 (0.01) | |

conductance, we estimated the transference number for calcium ($t_{Ca}=g_{Ca}/g_m$) by assuming that under the conditions measured, the only two permeant ions were $Cl^-$ and $Ca^{2+}$. This was done by measuring the diffusion potential at different $CaCl_2$ concentrations (see materials and methods). The diffusion potential was a linear function of the log of the activity ratio (log $a_{cis}/a_{trans}$) across the membrane in synthetic and

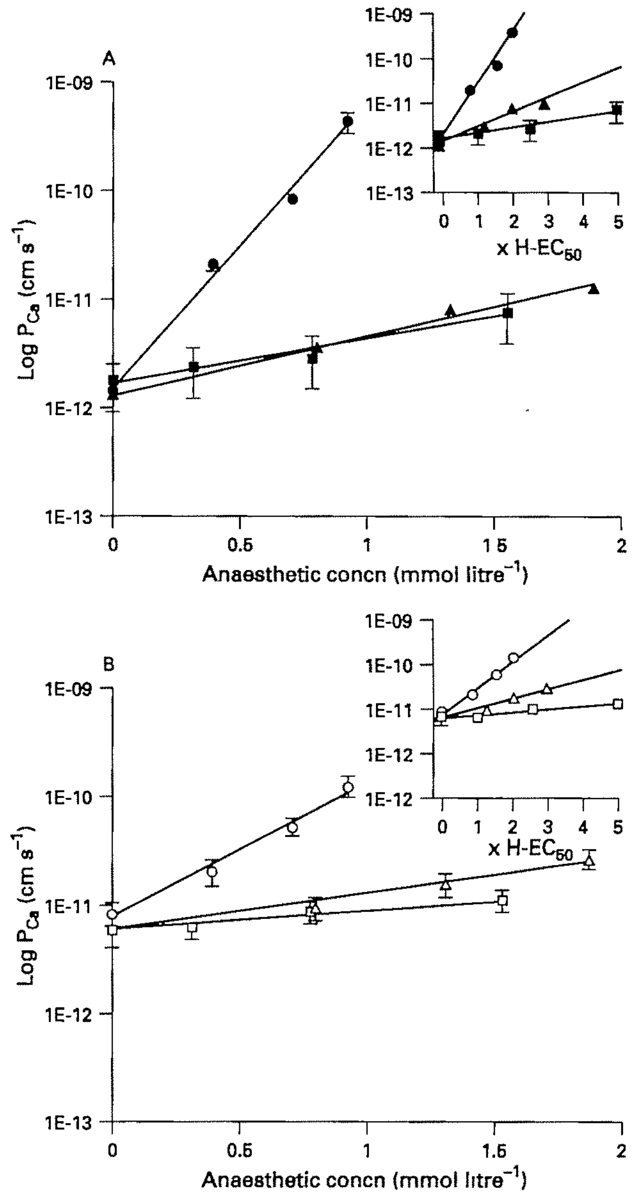

*Figure 4* Effect of volatile anaesthetics on calcium permeability in membranes formed with synthetic (A) and L-SR-extracted lipids (B). The log of membrane calcium permeability ($P_{Ca}$) was plotted against the anaesthetic concentration in the aqueous solution in mmol $litre^{-1}$ and against the ratio of the hypothetical-aqueous concentration (xH-$EC_{50}$) corresponding to the hypothetical MAC at 25°C (insets). The number of membranes used are the same as in figure 2. Data were fitted to a single exponential function. The fits of the data collected in membranes formed with synthetic lipids gave the following values: $y=1\ 66\times10^{-12}\times10^{2\ 49\times X}$ ($r^2=0.99$), $y=1.65\times10^{-12}\times10^{0\ 37\times X}$ ($r^2=0.97$), and $y=1.34\times10^{-12}\times10^{0\ 50\times X}$ ($r^2=0.99$) for isoflurane (●), halothane (■) and enflurane (▲), respectively, for log $P_{Ca}$ *vs* mmol $litre^{-1}$; and $y=1.66\times10^{-12}\times10^{1.17\times X}$ ($r^2=0.99$), $y=1.65\times10^{-12}\times10^{0\ 12\times X}$ ($r^2=0.97$) and $y=1.34\times10^{-12}\times10^{0\ 33\times X}$ ($r^2=0.99$) for isoflurane, halothane and enflurane, respectively, for log $P_{Ca}$ *vs* xH-$EC_{50}$. The fits of the data collected in membranes formed with L-SR-extracted lipids gave the following values: $y=7.39\times10^{-12}\times10^{1\ 20\times X}$ ($r^2=0.98$), $y=5.80\times10^{-12}\times10^{0\ 14\times X}$ ($r^2=0.87$) and $y=5.60\times10^{-12}\times10^{0\ 30\times X}$ ($r^2=0.97$) for isoflurane (○), halothane (□) and enflurane (△), respectively, for log $P_{Ca}$ *vs* mmol $litre^{-1}$; and $y=7.39\times10^{-12}\times10^{0\ 56\times X}$ ($r^2=0.98$), $y=5.80\times10^{-12}\times10^{0\ 04\times X}$ ($r^2=0.87$) and $y=5.60\times10^{-12}\times10^{0\ 20\times X}$ ($r^2=0\ 97$) for isoflurane, halothane and enflurane, respectively, for log $P_{Ca}$ *vs* xH-$EC_{50}$. Data points represent mean (SEM). The observed increases in $P_{Ca}$ were significant at all doses of volatile anaesthetic except that observed at the lowest dose of halothane in membranes formed with L-SR-extracted lipids.

L-SR-extracted lipids and intercepted 0 at both axes, as is expected for diffusion potentials (fig. 3). Figure 3 also indicates the diffusion potential for a purely chloride-selective membrane and a purely calcium-selective membrane. The diffusion potentials of membranes formed with synthetic lipids were closer to the values expected for a purely chloride-selective membrane than the diffusion potentials of membranes formed with L-SR-extracted lipids. In fact, the calculated $t_{Ca}$ value was larger in membranes formed with L-SR-extracted lipids than in membranes formed with synthetic lipids (table 3).

The volatile anaesthetics did not produce significant changes in $t_{Ca}$ (table 4). Therefore, volatile anaesthetics induced an increase in $g_m$ without changing the ionic selectivity of the membrane pathway. Figure 3 shows that the diffusion potential changed linearly with log $(a_{cis}/a_{trans})$, indicating that the $t_{Ca}$ values are similar at various concentration gradients.

### CALCIUM CONDUCTANCE AND PERMEABILITY OF LIPID MEMBRANES

Specific calcium conductance $(g_{Ca})$ and permeability $(P_{Ca})$ were estimated in $CaCl_2$ 200 mmol $litre^{-1}$ by assuming that the proton and hydroxide conductances were negligible, and by using equations (4) and (5):

$$g_{Ca}=g_m t_{Ca} \qquad (4)$$

$$P_{Ca}=RTg_{Ca}/(z^2F^2[Ca^{2+}]) \qquad (5)$$

where $z$=valence of calcium, $[Ca^{2+}]$=concentration of calcium (mol $cm^{-3}$). $g_{Ca}$ and $P_{Ca}$ values were approximately 4.5 times larger in membranes formed with L-SR-extracted lipids than in membranes formed with synthetic lipids (table 4). Volatile anaesthetics did not affect $t_{Ca}$ (table 4) but increased $P_{Ca}$ (fig. 4). The observed increase in $P_{Ca}$ was therefore caused by an increase in $g_m$ (fig. 2) rather than a change in ionic selectivity (table 4). Isoflurane produced the largest increase in $P_{Ca}$, the effects of enflurane and halothane were smaller.

### MEMBRANE CONDUCTANCE IN THE PRESENCE OF SUCROSE 0.6 MOL $LITRE^{-1}$

Total membrane conductance measured in $CaCl_2$ $(g_m)$ is the sum of the conductance for each ion present in the bath solution. We attempted to estimate the contribution of proton–hydroxide conductance to total membrane conductance by measuring membrane conductance in the presence of symmetrical solutions of sucrose 0.6 mol $litre^{-1}$. In the absence of volatile anaesthetic, $g_{msucr}$ and $g_m$ were the same (fig. 5). Isoflurane increased $g_{msucr}$ of membranes in a dose-dependent manner (fig. 5). However, the isoflurane-induced increase in $g_{msucr}$ was approximately 25% of the isoflurane-induced increase in $g_m$. This indicates that volatile anaesthetics induce an increase not only in $P_{H^+OH^-}$ but also in $P_{Ca}$ or $P_{Cl}$, or both. If one assumes that $g_{msucr}$ is only a result of $P_{H^+OH^-}$ then $g_m$ of these membranes in the absence of volatile anaesthetic should be entirely a result of $P_{H^+OH^-}$. This is unlikely as we were able to measure diffusion potentials in gradients of $CaCl_2$ and in the absence of a gradient for $H^+$ and $OH^-$. There are two possible explanations why in the absence of volatile anaesthetic, $g_m$ was equal to $g_{msuc}$. First, sucrose could increase $P_{H^+OH^-}$ and second, $CaCl_2$ could decrease $P_{H^+OH^-}$.

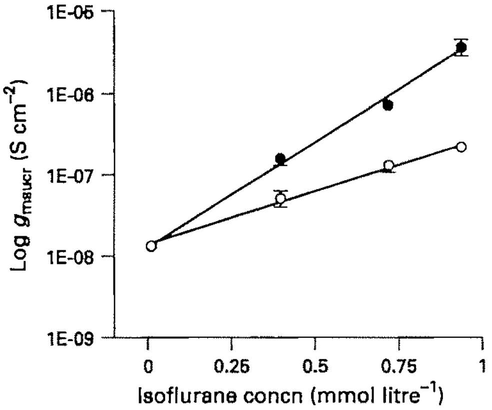

*Figure 5* Effect of isoflurane on total specific membrane conductance in sucrose. The total specific membrane conductance in sucrose $(g_{msucr})$ was measured in symmetrical solutions of sucrose 0.6 mol $litre^{-1}$ in membranes formed with synthetic lipids (electrodes with salt bridges). $g_{msucr}$ was plotted against the anaesthetic concentration in the bath solution (mmol $litre^{-1}$). Data were fitted to a single exponential function. The fits of the data collected in sucrose 0 6 mol $litre^{-1}$ (○) gave the following values: $y=1.43\times10^{-8}10^{1\ 28\times X}$ $(r^2=0.99)$ (four membranes). ●=Data collected in $CaCl_2$ solutions shown in figure 2A: $y=1.31\times10^{-8}\times10^{2\ 53\times X}$ $(r^2=0.99)$.

## Discussion

At the concentrations studied, we found that volatile anaesthetics increased $g_{Ca}$ and $g_{Cl}$ without affecting ionic selectivity or specific capacitance of planar lipid bilayers. We found also that volatile anaesthetics induced a significant increase in $P_{Ca}$ of lipid membranes, such an increase depended on the lipid composition, but its magnitude was too small to account for the previously reported volatile anaesthetic-induced increase in $Ca^{2+}$ leakage in isolated L-SR vesicles.

### MEMBRANE SPECIFIC CAPACITANCE

Membranes formed with L-SR-extracted lipids and synthetic lipids containing negatively charged phospholipids were smaller and had higher specific capacitance values than membranes formed with synthetic neutral lipids. Therefore, at least in the presence of high $Ca^{2+}$ concentrations, negatively charged phospholipids appear to be responsible, in part, for the formation of a larger membrane torus (smaller membrane area) and providing the membrane with a higher specific capacitance value.

A potential artefact in our capacitance measurements might result from residual decane in the lipid phase. This was unlikely because the specific capacitance values obtained in this study were similar to those reported previously for biological cell membranes.[31] Moreover, it has been reported that when actual membrane areas are measured, decane does not significantly affect membrane thickness and it appears to accumulate mainly at the membrane

*Table 5* Calcium currents ($I_{Ca}$) in the absence and presence of volatile anaesthetic *The concentrations of volatile anaesthetic were: halothane 1.54, enflurane 1.88 and isoflurane 0.94 mmol litre$^{-1}$. **This value was calculated using Ca$^{2+}$ leakage measurements from SR of skinned cardiac myocytes (1.24 mmol litre$^{-1}$)[33] in the absence of ATP and anaesthetic. It was assumed that cell volume was 24 pl, SR volume per myocyte was 8 4 pl and SR surface area per myocyte was 29 28×10$^3$ μm$^2$.[34] ***This value was calculated from Ca$^{2+}$ leakage measured in isolated L-SR-vesicles from skeletal muscle after ATP depletion.[1] It was assumed that 1 mg protein from L-SR membranes corresponded to 2.8×10$^3$ cm$^2$ SR membrane area[35]

| | $I_{Ca}$(mol cm$^{-2}$s$^{-1}$) |
|---|---|
| Synthetic lipid | $2.0\times10^{-17}$ |
| L-SR-extracted lipid | $8.3\times10^{-17}$ |
| L-SR-extracted lipid+halothane* | $11\ 2\times10^{-17}$ |
| L-SR-extracted lipid+enflurane | $26.5\times10^{-17}$ |
| L-SR-extracted lipid+isoflurane | $137.0\times10^{-17}$ |
| SR in skinned muscle cells** | $5.9\times10^{-13}$ |
| Isolated L-SR-vesicles*** | $3–11\times10^{-14}$ |

torus.[20] The lack of a volatile anaesthetic effect on either membrane area or specific capacitance indicates that, at the concentrations studied, volatile anaesthetics did not affect membrane geometry.

## MEMBRANE CONDUCTANCE AND $\mathrm{T_{Ca}}$ VALUES

Total membrane conductance ($g_m$) and Ca$^{2+}$ selectivity ($t_{Ca}$) was higher in membranes formed with L-SR-extracted lipids than in membranes formed with synthetic neutral lipids. This difference reflects, in part, the presence of negatively charged lipids in the L-SR-extracted lipid preparation, as $g_m$ and $t_{Ca}$ values were higher in membranes formed with synthetic lipids containing negatively charged lipids than in those containing only neutral lipids (table 3). The higher $t_{Ca}$ value is consistent with previous observations that lipid membranes become more cationic-selective when they have negatively charged lipids.[24]

At the concentrations studied, volatile anaesthetics increased $g_m$ without changing the $t_{Ca}$ value of the membrane, that is volatile anaesthetics increased the rate of ion transport across the lipid membrane pathway without affecting the ionic selectivity of such a pathway. As there were no membrane proteins present, ion transport across these membranes must be determined by lipid interactions. Our study, however, did not allow the molecular mechanism of these interactions in the presence of volatile anaesthetics to be defined.

## ESTIMATION OF Ca LEAKAGE CURRENTS

The magnitude of the Ca$^{2+}$ leakage currents were estimated using the Goldman flux equation,[32] and by assuming that the transmembrane potential across the SR membrane was 5 mV, intraluminal and cytoplasmic Ca$^{2+}$ concentrations were 10 mmol litre$^{-1}$ and 0.1 μmol litre$^{-1}$, respectively, and that $P_{Ca}$ was not affected by changes in Ca$^{2+}$ ion concentration.

$$I_{Ca}=(-P_{Ca}2FE_m/RT)\times([Ca^{2+}]_m-[Ca^{2+}]_{out})\times \exp(-2FE_m/RT)/(1-\exp(-2FE_m/RT)$$

where $I_{Ca}$=Ca$^{2+}$ flux (mol cm$^{-2}$ s$^{-1}$), $E_m$= transmembrane potential (V) and $[Ca^{2+}]_m$ and $[Ca^{2+}]_{out}$=intraluminal and myoplasmic Ca$^{2+}$ concentrations (mol cm$^{-3}$), respectively. The estimated $I_{Ca}$ for lipid membranes are three or four orders of magnitude smaller than those estimated for SR in skinned cardiac myocytes[33] (table 5). The high Ca$^{2+}$ leakage value of SR in skinned cardiac myocytes could reflect the presence of non-selective ion channel proteins. Non-selective chloride channels that allow passage of Ca$^{2+}$ ions and contribute significantly to Ca$^{2+}$ leakage have been demonstrated in isolated SR vesicles.[36] If Ca$^{2+}$ leakage through the SR in intact cells is as high as that reported for SR in skinned cells, then the observed volatile anaesthetic-induced increase in ionic permeability of lipid membranes will not contribute significantly to the overall SR leakage currents.

Estimated Ca$^{2+}$ leakage from isolated L-SR-vesicles[1] was two or three orders of magnitude higher than that estimated for lipid membranes in the absence and presence of volatile anaesthetics (table 5). Measurements were performed at room temperature in lipid membranes (this study) and at 37 °C in isolated L-SR vesicles.[1] However, such differences in temperature are unlikely to account for the different Ca$^{2+}$ leakage values. In fact, it has been reported that in liposomes formed with SR-extracted lipids, increasing the temperature from 25 to 40 °C increased the rate constant of Ca$^{2+}$ efflux by less than one order of magnitude.[37] As discussed in the next section, our estimated $P_{Ca}$ values for lipid membranes, if anything, represent overestimations because of the differences in other experimental conditions (e.g. calcium concentration, pH, etc.). Therefore, Ca$^{2+}$ leakage from isolated L-SR vesicles, both in the absence and presence of volatile anaesthetic, involves paths other than SR membrane lipids. These paths may involve inhibition of Ca$^{2+}$ pump activity, Ca$^{2+}$ efflux through membrane proteins such as the Ca$^{2+}$ pump (slippage through ATPase channels)[19] or through ion channels other than Ca$^{2+}$ release channels (e.g. non-selective ion channels),[36] or Ca$^{2+}$ leakage through the protein–lipid interface (boundary lipids).

The volatile anaesthetic-induced increase in $P_{Ca}$ of lipid bilayers and in Ca$^{2+}$ leakage from L-SR vesicles showed different properties. While volatile anaesthetics increased the $P_{Ca}$ of lipid bilayers in a dose-dependent manner, such dose dependency was not observed for the volatile anaesthetic-induced increase in Ca$^{2+}$ leakage from L-SR vesicles. The volatile anaesthetic-induced increase in $P_{Ca}$ of lipid bilayers was greater for isoflurane than for halothane or enflurane. This potency difference was not observed for the volatile anaesthetic-induced increase in Ca$^{2+}$ leakage from L-SR vesicles. Therefore, the volatile anaesthetic-induced increase in $P_{Ca}$ of membranes formed with L-SR-extracted lipids did not appear to be directly responsible for the volatile anaesthetic-induced increase in non-specific Ca$^{2+}$ leakage from isolated L-SR vesicles. Indirectly, however, the observed volatile anaesthetic-induced increase in membrane $P_{Ca}$ may serve as a trigger to activate calcium release channels; the volatile anaesthetic-induced increase in SR membrane chloride permeability may increase the activation of non-selective ion channels,[36] and the $Ca^{2+}$ currents through these non-selective channels may also serve as a trigger for calcium release channels.

### EFFECTS OF THE EXPERIMENTAL CONDITIONS AND ASSUMPTIONS ON THE ESTIMATED $P_{Ca}$

In this study several assumptions were made when estimating $P_{Ca}$. First, that increases in $Ca^{2+}$ did not affect the $P_{Ca}$ of lipid membranes. At high concentrations $Ca^{2+}$ is known to bind to phospholipids and produce phase separation of lipid mixtures.[38–40] To our knowledge, however, there are no reports indicating that increases in $Ca^{2+}$ affect the $P_{Ca}$ of lipid membranes. Such increases in $Ca^{2+}$ would not be expected to decrease $P_{Ca}$, if anything they may increase $P_{Ca}$. Second, we used pH 6.0 to reduce proton conductance through lipid membranes. Changes in pH are known to strongly affect the function of membrane proteins, however, our experiments were performed in the absence of membrane proteins. In the absence of membrane proteins, ions permeate only through the lipid membrane. If $H^+$ and $Ca^{2+}$ are using the same lipid pathway, reduction of protons should lead to an increase in the conduction of calcium. In this case, $P_{Ca}$ is overestimated when using a low pH. Third, the assumption that $g_{HEPES}$ was negligible compared with $g_{Ca}$ and $g_{Cl}$ and the lack of correction for the contribution by $g_{H/OH}$ tends to overestimate the calculated $P_{Ca}$. The presence of decane in the lipid membranes should increase $P_{Ca}$. All of the above assumptions tend to overestimate $P_{Ca}$. In spite of this, our estimated control $P_{Ca}$ values agreed closely with those obtained with $Ca^{2+}$ flux measurements in liposomes formed with various phospholipids or SR-lipid extracts, in which low concentrations of $Ca^{2+}$ were used (1 mmol $litre^{-1}$), no decane was present, pH was 8.0 and flux measurements were not contaminated by $g_{H/OH}$.[37] These observations suggest that in the absence of proteins our estimated $P_{Ca}$ values were close to those obtained using lipid vesicles at low calcium concentration and pH 8.0,[37] and that under our conditions the contribution of $g_{H/OH}$ was not significant. Even if there is overestimation of $P_{Ca}$, our main conclusion remains valid, that is that the volatile anaesthetic-induced increases in $P_{Ca}$, although significant, were too small to account for the previously observed volatile anaesthetic-induced increases in $Ca^{2+}$ leakage in skinned SR and isolated L-SR vesicles (table 5). Therefore, membrane paths other than SR membrane lipids must be involved.

In SR membranes, plasmalogens (alkyl ester phospholipids) account for 72% of phosphatidylethanolamine (PE) and 12% of phosphatidylcholine (PC) (20% of total phopholipids).[14] In this study we used diacyl PE and PC because plasmalogens were not available commercially. To our knowledge there are no reports on how plasmalogens affect membrane ionic permeability. It is possible, therefore, that the presence of plasmalogens in membranes formed with L-SR-extracted lipids contributes in part to the differences observed between membranes formed with synthetic lipids and L-SR-extracted lipids.

Halothane which, of the volatile anaesthetics studied, is the most potent trigger of malignant hyperthermia, produced the smallest increase in $g_{Ca}$ of lipid membranes and hence the smallest predicted increase in cytoplasmic $Ca^{2+}$. The latter suggests that the halothane-induced increase in $P_{Ca}$ of SR lipid membranes by itself does not appear to account for halothane-induced malignant hyperthermia.

In summary, at the concentrations studied, volatile anaesthetics increased the rate of ion transport across lipid membranes without affecting the ionic selectivity of the membrane or its dimensions. The strongest effect was exhibited by isoflurane and the weakest effect by halothane; the effect of enflurane was intermediate. This volatile anaesthetic effect cannot account for the volatile anaesthetic-induced increase in $Ca^{2+}$ leakage observed in isolated L-SR vesicles.

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## Appendix

In our $CaCl_2$ solutions, the diffusion potential ($V_d$) or potential at which the current equals zero, was determined by the following equation:

$$V_d = g_{Ca}E_{Ca}/g_m + g_{Cl}E_{Cl}/g_m + g_{H/OH}E_{H/OH}/g_m + g_{HEPES}E_{HEPES}/g_m \quad (1)$$

where $g_{Ca}$=calcium conductance; $g_{Cl}$=chloride conductance; $g_{H/OH}$=proton–hydroxide conductance; $g_{HEPES}$=HEPES conductance; $E_{Ca}$, $E_{Cl}$, $E_{H/OH}$ and $E_{HEPES}$=equilibrium potentials (Nernst potential) for each of the ions As there was no pH or HEPES gradient, $E_{H/OH}$ and $E_{Hepes}$ are zero, and equation (1) becomes

$$V_d = t_{Ca}E_{Ca} + t_{Cl}E_{Cl} \quad (2)$$

where $t_{Ca}$=transference number for $Ca^{2+}$ and $t_{Cl}$=transference number for $Cl^-$ This equation can be rewritten as follows

$$V_d = -t_{Ca}\times(RT/2F)\times\ln([Ca^{2+}]_{cis}/[Ca^{2+}]_{trans}) + t_{Cl}(RT/F)\times\ln([Cl^-]_{cis}/[Cl^-]_{trans}) \quad (3)$$

$$V_d = (t_{Cl} - t_{Ca}/2)(RT/F)\times\ln([CaCl_2]_{cis}/[CaCl_2]_{trans}) \quad (4)$$

$$V_d = (t_{Cl} - t_{Ca}/2)(RT/F)\times\ln(a_{cis}/a_{trans}) \quad (5)$$

where $R$=gas constant; $T$=temperature in Kelvin scale, $F$=Faraday constant; $[]_{cis}$ and $[]_{trans}$=ion or salt concentration in the *cis* (front) and *trans* (back) compartments; $a_{cis}$ and $a_{trans}$=mean salt activity in the *cis* and *trans* compartments (interpolated from previously published values).[25] When assuming that only $Ca^{2+}$ and $Cl^-$ ions carry the current, then·

$$t_{Ca} + t_{Cl} = 1 \quad (6)$$

and equation (5) becomes·

$$V_d = (1 - 1.5t_{Ca})\times(RT/F)\times\ln(a_{cis}/a_{trans}) \quad (7)$$

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# Effects of magnesium sulphate on atrioventricular conduction times and surface electrocardiogram in dogs anaesthetized with sevoflurane

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## Summary

We have studied the effects of magnesium on atrioventricular (AV) conduction times and surface electrocardiogram during both sinus rhythm and atrial pacing in seven dogs anaesthetized with 1 MAC of sevoflurane. A bolus dose of magnesium sulphate ($MgSO_4$) 30, 60 and 90 mg kg$^{-1}$ significantly increased plasma magnesium concentrations from 1.3 (SEM 0.1) to 15.3 (1.3) mg dl$^{-1}$. $MgSO_4$ significantly prolonged A-H (AV nodal conduction time during sinus rhythm), St-H (intra-atrial and AV nodal conduction time during atrial pacing) and H-S (total ventricular conduction time) intervals at doses $\geq$30 mg kg$^{-1}$ ; H-V interval (His–Purkinje conduction time) at doses $\geq$60 mg kg$^{-1}$; RR and PR intervals and QRS duration at doses $\geq$30 mg kg$^{-1}$ in a dose-related manner during both sinus rhythm and atrial pacing. QTc interval remained unchanged during sinus rhythm. The doses of $MgSO_4$ used did not have deleterious effects on AV conduction times and surface electrocardiogram during 1 MAC of sevoflurane anaesthesia. This finding suggests that $MgSO_4$ in high doses was safe and may be indicated for cardiac arrhythmia and hypertension during sevoflurane anaesthesia. However, further study is required to apply these findings to clinical anaesthesia. (*Br. J. Anaesth.* 1997; **78**: 000–000)

**Key words**
Anaesthetics volatile, sevoflurane. Heart, conduction. Monitoring, electrocardiography. Pharmacology, magnesium sulphate.

Magnesium has been used i.v. for several decades for the treatment of cardiac arrhythmias, such as paroxysmal atrial tachycardia, atrial fibrillation and ventricular extrasystoles associated with digitalis intoxication[1–3] and it has also been shown to be an effective anti-arrhythmic in a variety of cases of QT interval prolongation and torsades de pointes.[4 5] Recently, magnesium sulphate has been reported to have cardiac electrophysiological effects that explain its ability to suppress bupivacaine-induced cardiac arrhythmias in dogs.[6]

Inhalation anaesthetics affect specialized atrioventricular (AV) conduction: enflurane and halothane are more depressant on AV conduction times than isoflurane.[7] The electrophysiological effects of sevoflurane, however, have not been examined fully. Comparing the effects of 1 and 2 MAC of sevoflurane, isoflurane and halothane on specialized AV conduction times in dogs anaesthetized with pentobarbitone, we have found previously that both sevoflurane and isoflurane did not affect AV conduction times, whereas halothane significantly prolonged atrio-His conduction time.[8]

Magnesium salts could be used during inhalation anaesthesia because of their anti-arrhythmic and antihypertensive properties. Although the electrophysiological and electrocardiographic effects of i.v. administered magnesium salts have been studied in animals[9 10] and in humans,[11 12] the effects of magnesium on the cardiac conduction system have not been studied during inhalation anaesthesia. Therefore, we have investigated the effects of magnesium sulphate on AV conduction times and surface electrocardiogram in dogs anaesthetized with sevoflurane.

## Materials and methods

### ANIMAL PREPARATION

The study was approved by the management committee at the Jichi Medical Laboratory of Experimental Medicine, based on the school's *Guide for Laboratory Animals*, 1993.

Anaesthesia was induced in seven mongrel dogs, weighing 13–18 kg, with 3-5% sevoflurane via a funnel-shaped plastic mask fitted to the dog's face and connected to a Jackson–Rees circuit. The trachea was intubated without neuromuscular blocking agents and ventilation was adjusted to maintain normocapnia with a Harvard pump respirator (R-60, Aika, Co., Ltd). Anaesthesia during surgical preparation was maintained with 2–3% end-tidal concentrations of sevoflurane and 50% nitrous oxide in oxygen delivered into an inspiratory limb of a Harvard pump respirator. Sevoflurane was vaporized

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with a Sevotec vaporizer (Penlon Inst., Ltd) and end-tidal concentrations of sevoflurane were measured with a calibrated respiratory gas analyser (Model 5250, Ohmeda). A micromanometer-tipped catheter (7F 45326, Toyoda Instr, Ltd) was placed through the left femoral artery into the abdominal aorta to measure systolic, diastolic and mean arterial pressures (SAP, DAP and MAP, respectively). A catheter was inserted into the abdominal aorta via the right femoral artery to sample arterial blood for measurement of pH, $Pa_{O_2}$, $Pa_{CO_2}$, and serum $Na^+$, $K^+$ and $Ca^{2+}$ concentrations (288 Blood Gas System, Ciba Corning). Plasma total magnesium and calcium concentrations were measured by colorimetric assay. Lactated Ringer's solution was infused at 5–10 ml $kg^{-1}$ $h^{-1}$ into the left femoral vein throughout the experiment. Arterial blood pH was adjusted to the normal range by i.v. administration of sodium bicarbonate. KCl solution was given to maintain serum $K^+$ concentration between 3.5 and 4.5 mmol $litre^{-1}$. Body temperature was measured with an oesophageal thermistor and maintained at 36–37 °C using an external heating blanket.

A 6F quadripolar electrode catheter was inserted via the left internal carotid artery and advanced towards the aortic root until a stable His-bundle electrogram (HBE) was obtained as displayed on an oscilloscope.[13] The His-bundle catheter electrodes were connected to a switch box that allowed selection of any combination of two electrodes. The output of the switch box was connected to a pre-amplifier with a bandwidth cut-off frequency of 40–1000 Hz. The electrodes of the surface ECG (lead II and $V_5$) were connected to another pre-amplifier with a filter bandwidth of 0.1–120 Hz. The output from each preamplifier was recorded onto a thermal recorder (8M15, NEC San-ei, Ltd, Tokyo, Japan) at a paper speed of 100 mm $s^{-1}$. Arterial pressures and surface ECG were recorded on a multi-channel recorder (Recti-Horiz-8K, NEC San-ei, Ltd, Tokyo, Japan). Heart rate was measured by counting QRS complexes over 10 s.

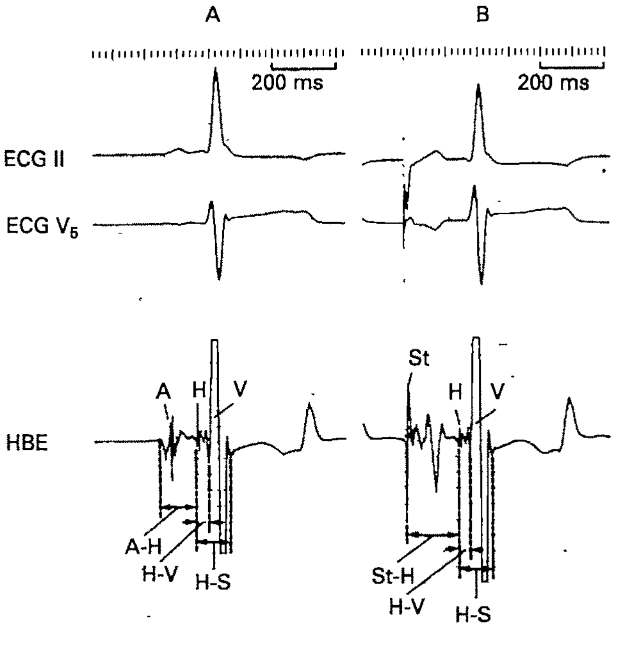

*Figure 1* Surface electrocardiograms (ECG) (leads II and $V_5$) and His-bundle electrogram (HBE) during sinus rhythm (A) and atrial pacing (B). A=Atrial deflection; H=His-bundle spike; V=ventricular deflection; St=stimulus artefact; A-H (atrioventricular (AV) nodal conduction time during sinus rhythm)=interval from atrial deflection to the beginning of the His-bundle spike in the HBE; St-H (intra-atrial and AV nodal conduction time during atrial pacing)=interval from stimulus artefact (St) to the beginning of the His-bundle spike in the HBE; H-V (His–Purkinje conduction time)=interval from the beginning of the His-bundle spike to the beginning of ventricular deflection in the HBE; H-S (ventricular conduction time)=interval from the beginning of the His-bundle spike to the end of rapid ventricular deflection in the HBE.

HBE was recorded at a paper speed of 500 mm $s^{-1}$ to calculate AV conduction intervals with 1.0-ms resolution (Visigraph 5L37, NEC San-ei, Ltd, Tokyo, Japan). Another 6F quadripolar electrode catheter was inserted into the right atrium via the right femoral vein for atrial pacing. An R-wave coupled cardiac stimulator (3F61, NEC San-ei, Instr., Ltd) delivering a rectangular monophasic pacing impulse of 1 ms duration was used for all atrial pacing. The stimulating current used was twice the threshold determined at the control state.

RR and PR intervals, QRS duration and QT interval were measured from ECG lead II. QT interval was corrected for heart rate by dividing the QT interval by the square root of the RR interval to obtain the QTc interval.[14]

AV conduction times measured in this study were as follows: A-H interval (AV nodal conduction time during sinus rhythm), St-H interval (intra-atrial and AV nodal conduction time during atrial pacing), H-V interval (His–Purkinje conduction time) and H-S interval (total ventricular conduction time). A-H interval was measured from the beginning of atrial deflection to the beginning of the His-bundle spike in the HBE.[15] The St-H interval was measured from the beginning of the stimulus artefact (St) to the beginning of the His-bundle spike in the HBE.[16] The H-V interval was measured from the beginning of the His-bundle spike to the beginning of ventricular deflection in the HBE.[15] The H-S interval was measured from the beginning of the His-bundle spike to the end of the rapid deflection in the HBE (fig. 1).[16]

## EXPERIMENTAL PROCEDURE

At the end of the surgical procedure, nitrous oxide was discontinued and the end-tidal concentration of sevoflurane was adjusted to 2.4% (1 MAC) and maintained for at least 20 min. After haemodynamic stabilization, control values of the variables mentioned above were obtained during both sinus rhythm and subsequent atrial pacing. The right atrium was paced constantly at 86 (7) beat $min^{-1}$ (paced cycle length of 708.6 (65.6) ms), which was slightly higher than control sinus rate during each administration of magnesium sulphate ($MgSO_4$). Twenty beats were recorded during sinus rhythm, and then the right atrium was paced for 1 min and 20 consecutive beats were recorded. Sinus rhythm returned immediately after pacing was discontinued.

All dogs were given a 10% solution of $MgSO_4$ in a bolus of 30, 60 and 90 mg kg$^{-1}$ at 15-min intervals. All measurements and blood sampling were performed 1–2 min after each administration of $MgSO_4$ during both sinus rhythm and subsequent atrial pacing.

### STATISTICAL ANALYSIS

Statistical analysis was performed using analysis of variance with repeated measures, followed by Fisher's protected least significant difference (PLSD). $P<0.05$ was considered statistically significant. Data are given as mean (SEM).

## Results

### CHANGES IN BLOOD ELECTROLYTE CONCENTRATIONS (TABLE 1)

Plasma total magnesium concentrations increased significantly from a control value of 1.3 (0.1) to 4.1 (0.3), 8.0 (0.8) and 15.3 (1.3) mg dl$^{-1}$ after $MgSO_4$ 30, 60 and 90 mg kg$^{-1}$, respectively. Plasma total calcium concentrations increased significantly at doses of $MgSO_4$ ≥30 mg kg$^{-1}$ ($P<0.05$) with no changes in serum $Ca^{2+}$ concentrations. Serum $K^+$ concentrations remained within the normal range.

### HAEMODYNAMIC EFFECTS (TABLE 2)

SAP, DAP, MAP and HR decreased significantly at doses ≥30 mg kg$^{-1}$ in a dose-related manner ($P<0.05$). Atrial pacing produced significant increases in SAP, DAP and MAP compared with each corresponding value obtained during sinus rhythm at 90, 30 and 30 mg kg$^{-1}$, respectively.

### ELECTROPHYSIOLOGICAL EFFECTS (TABLE 3)

$MgSO_4$ significantly prolonged A-H and St-H intervals at doses ≥30 mg kg$^{-1}$; H-V interval at doses ≥60 mg kg$^{-1}$ and H-S interval at doses ≥30 mg kg$^{-1}$ in a dose-related manner during both sinus rhythm and atrial pacing. There were no significant differences in AV conduction times between those obtained during sinus rhythm and atrial pacing. Atrial pacing rate was 86 (7) beat min$^{-1}$ (paced cycle length of 708.6 (65.6) ms), slightly greater than the control rate at sinus rhythm (82 (7) beat min$^{-1}$).

### ELECTROCARDIOGRAPHIC EFFECTS (TABLE 4)

RR and PR intervals were prolonged significantly at doses ≥30 mg kg$^{-1}$ during sinus rhythm. Significant differences were found in RR intervals between those obtained during sinus rhythm and atrial pacing at each dose of $MgSO_4$. QRS duration was prolonged significantly at doses ≥30 mg kg$^{-1}$ during sinus rhythm and at doses ≥60 mg kg$^{-1}$ during atrial pacing. The QT interval was prolonged significantly at doses ≥30 mg kg$^{-1}$ during both sinus rhythm and atrial pacing. The QTc interval remained unchanged during sinus rhythm and was significantly prolonged

*Table 1* Changes in blood electrolyte concentrations before and immediately after administration of magnesium sulphate (Mg $SO_4$) (mean (SEM)). Mg=Plasma total magnesium concentration; Ca=plasma total calcium concentration; $Ca^{2+}$=serum ionized calcium concentration; $K^+$=serum potassium concentration. Concentrations of Mg (mmol litre$^{-1}$) were calculated from the measured plasma concentrations of Mg (mg dl$^{-1}$). Significant differences compared with: control (*$P<0.05$, **$P<0.01$); preceding values (††$P<0.01$)

| | | $MgSO_4$ | | |
|---|---|---|---|---|
| | Control | 30 mg kg$^{-1}$ | 60 mg kg$^{-1}$ | 90 mg kg$^{-1}$ |
| Mg (mg dl$^{-1}$) | 1.3 (0.1) | 4.1 (0.3)** | 8.0 (0.5)**†† | 15 3 (1.3)**†† |
| Mg (mmol litre$^{-1}$) | 0.6 (0.1) | 1.7 (0.1)** | 3.3 (0.2)**†† | 6.3 (0 6)**†† |
| Ca (mg dl$^{-1}$) | 8.9 (0.3) | 9.5 (0.3)* | 10.1 (0.2)**†† | 11.0 (0.3)**†† |
| $Ca^{2+}$ (mmol litre$^{-1}$) | 1.18 (0.04) | 1.17 (0.07) | 1.18 (0.04) | 1.12 (0.03) |
| $K^+$ (mmol litre$^{-1}$) | 3.7 (0.1) | 3.7 (0.1) | 3.6 (0.1) | 3.7 (0.1) |

*Table 2* Effects of magnesium sulphate ($MgSO_4$) on arterial pressures and heart rate (mean (SEM)). SAP=Systolic arterial pressure; DAP=diastolic arterial pressure; MAP=mean arterial pressure; HR=heart rate; S=values obtained during sinus rhythm; P=values obtained during atrial pacing. Significant differences compared with· control (*$P<0.05$, **$P<0.01$); preceding values (†$P<0.05$, ††$P<0.01$); corresponding values during sinus rhythm (‡$P<0.05$, ‡‡$P<0.01$)

| | | $MgSO_4$ | | |
|---|---|---|---|---|
| | Control | 30 mg kg$^{-1}$ | 60 mg kg$^{-1}$ | 90 mg kg$^{-1}$ |
| SAP (mm Hg) | | | | |
| S | 120 (6) | 106 (5)** | 91 (4)**†† | 78 (6)**†† |
| P | 120 (6) | 110 (5)** | 97 (3)**†† | 86 (5)**††‡ |
| DAP (mm Hg) | | | | |
| S | 76 (3) | 62 (3)** | 51 (3)**†† | 44 (3)**†† |
| P | 77 (3) | 67 (3)**‡‡ | 57 (3)**††‡‡ | 50 (3)**††‡‡ |
| MAP (mm Hg) | | | | |
| S | 91 (3) | 76 (3)** | 64 (3)**†† | 55 (4)**†† |
| P | 91 (3) | 81 (3)**‡ | 70 (3)**††‡‡ | 62 (4)**††‡‡ |
| HR (beat min$^{-1}$) | | | | |
| S | 82 (7) | 78 (7)* | 71 (6)**† | 64 (6)**† |
| P | — | 86 (7)‡‡ | 86 (7)‡‡ | 86 (7)‡‡ |

*Table 3* Effects of magnesium sulphate ($MgSO_4$) on atrioventricular conduction times during sinus rhythm and atrial pacing (mean (SEM)). A-H interval=atrioventricular (AV) nodal conduction time; St-H interval=intra-atrial and AV nodal conduction time during atrial pacing; H-V interval=His–Purkinje conduction time; H-S interval=total ventricular conduction time; S=values obtained during sinus rhythm; P=values obtained during atrial pacing Significant differences compared with: control (*$P<0.05$, **$P<0.01$); preceding values (†$P<0.05$, ††$P<0.01$); no significant differences between S and P groups

| | | $MgSO_4$ | | |
|---|---|---|---|---|
| | Control | 30 mg $kg^{-1}$ | 60 mg $kg^{-1}$ | 90 mg $kg^{-1}$ |
| A-H interval (ms) | | | | |
| S | 84.3 (2.4) | 92.6 (3.2)* | 102.1 (5.1)**† | 119.9 (6.9)**†† |
| P | — | — | — | — |
| St-H interval (ms) | | | | |
| S | — | — | — | — |
| P | 115.6 (8 9) | 126.1 (10.0)** | 133.9 (8.9)**† | 157.1 (11.4)**†† |
| H-V interval (ms) | | | | |
| S | 37.0 (1.8) | 39.6 (2.4) | 43.9 (3.0)**†† | 47.4 (2.3)**† |
| P | 37.1 (2.6) | 38 9 (2.3) | 44.1 (3.0)**†† | 48.0 (2.9)**† |
| H-S interval (ms) | | | | |
| S | 110.7 (4 1) | 116.7 (4.4)* | 122.9 (4.7)**† | 132.4 (2.8)**†† |
| P | 112.9 (4.7) | 117.4 (4.3)* | 122.9 (3.6)**† | 129.9 (3.1)**†† |

*Table 4* Effects of magnesium sulphate ($MgSO_4$) on electrocardiographic variables during sinus rhythm and atrial pacing (mean (SEM)). QTc interval=QT interval/√RR (s); S=values obtained during sinus rhythm; P=values obtained during atrial pacing. Significant differences compared with: control (*$P<0.05$, **$P<0.01$); preceding values (†$P<0.05$, ††$P<0.01$); corresponding values during sinus rhythm (‡$P<0.05$, ‡‡$P<0.01$)

| | | $MgSO_4$ | | |
|---|---|---|---|---|
| | Control | 30 mg $kg^{-1}$ | 60 mg $kg^{-1}$ | 90 mg $kg^{-1}$ |
| RR interval (ms) | | | | |
| S | 746.4 (63.5) | 802.9 (63.8)* | 860.7 (67.2)**† | 961 4 (70.4)**†† |
| P | 708.6 (65.6) | 708.6 (65.6)‡‡ | 708.6 (65 6)‡‡ | 708.6 (65.6)‡‡ |
| PR interval (ms) | | | | |
| S | 118.0 (5.0) | 127.1 (5.0)* | 139.9 (6.4)**†† | 160.0 (5.0)**†† |
| P | — | — | — | — |
| QRS duration (ms) | | | | |
| S | 80.0 (6.7) | 84.3 (7.8)* | 88 4 (7.9)**† | 92.4 (8.5)**†† |
| P | 79.3 (7.4) | 82.3 (7.1) | 87.9 (7.7)**† | 92.4 (8.2)**† |
| QT interval (ms) | | | | |
| S | 360.0 (19.8) | 372.9 (20.5)* | 388.6 (21.0)**†† | 411.4 (24.0)**†† |
| P | 352.1 (20.2) | 367 1 (21.0)* | 380.0 (21.4)**† | 397.9 (23.8)**††‡ |
| QTc interval (ms) | | | | |
| S | 417.4 (16.0) | 422.8 (17 0) | 422.8 (13.7) | 421.5 (15.1) |
| P | 420.7 (12.1) | 438.6 (13.8)* | 454.5 (15.3)**†‡‡ | 475.6 (17.0)**†‡‡ |

at doses ≥30 mg $kg^{-1}$ during atrial pacing. No changes in ST segment or T wave were observed and detrimental AV conduction block and arrhythmias did not occur at any dose of $MgSO_4$ throughout the study.

## Discussion

Magnesium sulphate 30, 60 and 90 mg $kg^{-1}$ i.v. produced acute hypermagnesaemia with 4–12-fold increases in plasma total magnesium concentrations compared with control values. Magnesium sulphate significantly decreased heart rate and prolonged cardiac conduction times and electrocardiographic variables, except for QTc interval during sinus rhythm, with 1 MAC of sevoflurane anaesthesia. Arterial pressures decreased in a dose-dependent manner.

A decrease in heart rate and prolongation of A-H interval caused by magnesium sulphate are consistent with results of previous studies *in vitro*[17] and *in vivo*.[18] It has been shown that $Mg^{2+}$ is a naturally occurring $Ca^{2+}$ antagonist[19 20] which reduces movement of extracellular $Ca^{2+}$ into the myocardial cell by a competitive process localized at the sarcolemmal membrane.[21] In addition, intracellular $Mg^{2+}$ has been shown to block outward movement of $K^+$ through potassium channels.[22] Therefore, the negative chronotropic and dromotropic effects of magnesium can be attributed to its blocking effects on calcium and potassium currents involved in the genesis of the action potential in sinoatrial[23] and atrioventricular (AV) node cells.[24]

In this study, A-H and H-V intervals were prolonged almost in parallel with increases in doses of $MgSO_4$ during sinus rhythm. This finding is consistent with previous results obtained in an isolated canine heart by Molter and colleagues.[25] In their study, both A-H and H-V intervals increased significantly at serum magnesium concentrations up to 6 mmol $litre^{-1}$, although the magnitude of this effect was greater for A-H interval. A serum $Mg^{2+}$ concentration of 6 mmol $litre^{-1}$ corresponds to a peak mean value of serum total magnesium concentration of 15.3 mg $dl^{-1}$, measured after $MgSO_4$ 90 mg $kg^{-1}$ in this study. Although actual serum $Mg^{2+}$ concentrations 1–2 min after bolus administration of each dose of $MgSO_4$ were unclear, these results suggest that both AV node cells and Purkinje fibres may be equally sensitive to the depressant effects of $Mg^{2+}$. In humans, however, magnesium has been shown not to affect H-V conduction.[11,12] These differences may be attributed to low peak serum magnesium concentrations in their study.

$Mg^{2+}$ has been shown to reduce conduction velocity of cardiac cells via a decrease in maximum upstroke velocity by blocking the Na channel,[17,26] although the relation between upstroke velocity and conduction velocity may not be as direct as has been thought.[27] Because Purkinje fibres and ventricular muscle have almost the same ionic mechanisms for development of an action potential, with conduction velocities dependent on the rate of rise of depolarization carried by the fast inward $Na^+$ current, significant prolongation of H-V and H-S intervals during both sinus rhythm and atrial pacing may be explained by the $Na^+$ current blocking action of $Mg^{2+}$.

Prolongation of A-H and H-S intervals during both sinus rhythm and atrial pacing is thought to be responsible for electrocardiographic prolongation of P-R intervals during sinus rhythm and QRS duration during both sinus rhythm and atrial pacing, respectively.

QT interval reflects the average action potential duration (APD) of ventricular muscle and is determined mainly by the balance between outward $I_k$ and inward $I_{Ca}$ during ventricular repolarization.[28] Because QTc interval remained unchanged in this study, significant prolongation of QT interval during sinus rhythm can be attributed to dose-related decreases in heart rate. Although the precise mechanism for the effects of $Mg^{2+}$ on APD is unclear, this study suggested that calculated external $Mg^{2+}$ in the range 1.7 to 6.3 mmol litre$^{-1}$ did not affect the balance between outward $I_k$ and inward $I_{Ca}$ during repolarization with sevoflurane anaesthesia. While significant prolongation of QTc interval during atrial pacing may be attributed to decreases in R-R intervals induced with higher pacing rates than sinus rates, it is noteworthy that QT interval remained significantly prolonged during atrial pacing, as seen during sinus rhythm. A possible mechanism for this effect of $Mg^{2+}$ could be explained by impairment of an intracellular calcium-induced $I_{Ca}$ inactivation process.[29,30] Because $Mg^{2+}$ decreases $I_{Ca}$ through open channels during depolarization,[31,32] the increasing rates of ventricular depolarization induced with atrial pacing might not be accompanied by a sufficient increase in intracellular $Ca^{2+}$ concentration to activate the calcium-induced $I_{Ca}$ inactivation process and subsequently to shorten the plateau phase of APD, that is QT interval.

In this study, atrial pacing was performed to exclude the effects of heart rate on AV conduction times. The fact that the St-H interval was 30-40 ms longer than the A-H interval during sinus rhythm probably reflects the latency between stimulus and atrial activation. Because incremental increases in atrial-paced rates were not performed in this study, the effects of magnesium on the rate-dependence of AV nodal conduction times during sevoflurane anaesthesia were unclear.

The electrophysiological and electrocardiographic effects of sevoflurane have not been fully studied. Although autonomic system activity might be depressed to some extent by sevoflurane, 1 and 2 MAC of sevoflurane exerted no significant effects on heart rate or cardiac conduction times in pentobarbitone-anaesthetized dogs in our previous study.[8] Therefore, the direct effects of magnesium on the cardiac conduction system could predominate over the effect of sevoflurane on this system. Hatakeyama, Ito and Momose[33] reported that sevoflurane depressed overshoot and the upstroke velocity, and the plateau phase of action potentials at higher concentrations (>2.0%) without affecting resting membrane potential. These findings suggest that the electrophysiological interaction between sevoflurane and $Mg^{2+}$ may occur additively or synergistically through blocking actions on transmembrane $Na^+$ and $Ca^{2+}$ influx. It is not known if the electrophysiological effects of $MgSO_4$ are enhanced at higher concentrations than 1.0 MAC of sevoflurane.

To clarify the possible clinical electrophysiological risk of magnesium during sevoflurane anaesthesia, a battery of electrophysiological tests, including measurements of sinus node recovery time, AV nodal refractory periods and Wenckebach cycle length should be performed with lower (0 and 0.5 MAC) or higher (1.5 MAC and above) concentrations of sevoflurane. Although there were several limitations to our study mentioned above, our results suggest that magnesium should not exert adverse effects on AV conduction times during 1.0 MAC of sevoflurane anaesthesia.

In conclusion, serum concentrations of magnesium up to 15.3 mg dl$^{-1}$ did not produce detrimental electrophysiological or electrocardiographic effects in the presence of 1 MAC of sevoflurane. To apply these findings to clinical anaesthesia, however, further studies should be performed to examine the interaction between magnesium and anaesthetics for potential adverse effects that may occur on the electrophysiology of the heart.

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*British Journal of Anaesthesia* 1997; 78: 81–82

SHORT COMMUNICATIONS

# Prolonged peribulbar anaesthesia with indwelling catheter: a preliminary report of 217 cases†

J.-M. BERNARD AND J.-L. HOMMERIL

## Summary

We report a technique to prolong peribulbar anaesthesia by repetitive injections of lignocaine through a catheter in the inferotemporal peribulbar space during surgery anticipated to exceed 60 min. After peribulbar anaesthesia by standard percutaneous approach with the eye looking straight, a 19-gauge Tuohy needle was inserted backwards in the sagittal plane and parallel to the 5° slope of the orbit floor, to a distance of less than 3 cm, at the junction of the middle and lateral third of the lower orbital rim. A 23-gauge smooth catheter was advanced up to the tip of the needle which was withdrawn, keeping less than 3 cm of catheter in the inferotemporal compartment. A catheter was inserted in 217 consecutive patients undergoing vitrectomy, retinal detachment and retinal peeling. There were no technical difficulties. Neither additional sedation nor general anaesthesia was required during surgery, but less than 50% of patients requested lignocaine injections to supplement anaesthesia. Catheter insertion into the peribulbar space may represent a potential technique to perform a greater variety of ophthalmic surgery with regional anaesthesia. Indications should be limited to the longest procedures. (*Br. J. Anaesth.* 1997; **78**: 81–82)

**Key word**
Anaesthetic techniques, regional, peribulbar. Surgery, ophthalmological. Equipment, catheters.

Retrobulbar block has been used widely for various types of ophthalmic surgery; it consists of injection of a small volume of local anaesthetic into the extraocular muscle cone to anaesthetize the ciliary ganglion and nerves innervating the rectus muscles. However, as this technique involves blind insertion of a needle into a space occupied by delicate neural and vascular structures, complications can occur. With peribulbar injection, a larger volume of anaesthetic is injected with no attempt to enter the muscle cone which, at least theoretically, is less dangerous.[1 2] With time, the anaesthetic agent diffuses and adequate anaesthesia is obtained.

However, peribulbar block may be inadequate for prolonged procedures, such as posterior segment surgery. We describe a technique to prolong peribulbar anaesthesia by repetitive injections through a catheter in the inferotemporal peribulbar space.

## Methods and results

After local Institutional Human Investigation Committee review, we studied 217 consecutive ASA I–III patients undergoing ophthalmic surgery which was anticipated to exceed 60 min. During the preoperative visit, this aspect of anaesthetic management was explained and informed consent was obtained. Patients with impaired haemostasis or receiving oral anticoagulants and those with previous ipsilateral eye surgery were excluded. No premedication was given.

Peribulbar anaesthesia was produced initially by a standard percutaneous approach with the eye looking straight. Using a 27-gauge, 31-mm disposable retrobulbar needle, 5–8 ml of a 0.5% bupivacaine and 2% lignocaine mixture in equal proportion were injected into the inferotemporal compartment, followed 2 min later by a second injection for medial compartment peribulbar block. A bolus of propofol 0.5–1 mg $kg^{-1}$ i.v. was given to lessen the discomfort and awareness of the injection. Peribulbar block and consequently a peribulbar catheter technique should also be achievable after local anaesthesia of the inferotemporal conjunctival fornix, avoiding the need for propofol and preserving the advantages of local anaesthesia in very old and fragile patients.[3] Continuous decompression using a Honan balloon at a setting of 30 mm Hg was applied while patients recovered from propofol sedation.

Patients were asked to move their eyes, using maximal effort in the superior, inferior, medial and lateral directions. If globe akinesia was incomplete, a supplementary injection was given. When akinesia was complete, a 19-gauge Tuohy needle (Paediatric Extradural Set System 2, Rüsch Laboratory) was inserted under sterile conditions. The needle entry

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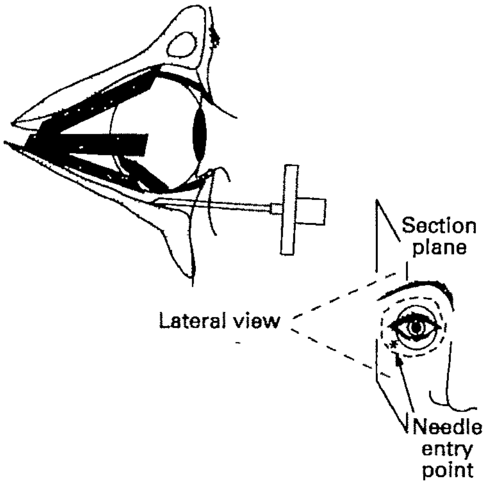

*Figure 1* Schematic drawing of the orbit after vertical section. Placement of the Tuohy needle as seen from the lateral view. The tip of the needle passed backwards in the sagittal plane and parallel to the 5° upward slope of the orbital floor. We recommend that a Tuohy needle with clear guide marks is used to avoid a depth greater than 3 cm from the orbital rim. *Needle entry point; inferotemporal approach at the junction of the middle and lateral third of the inferior orbital rim (broken line).

point was the junction of the middle and lateral third of the inferior orbital rim. Based on anatomical knowledge, the needle tip passed transcutaneous, backwards in the sagittal plane, parallel to the 5° upward slope of the orbit floor, less than 3 cm from the orbital rim (fig. 1). The initial peribulbar block probably pushed tissue and the eye away from the Tuohy needle, reducing the risk of penetration into the cone and into the globe. A 23-gauge smooth catheter was introduced and advanced up to the tip of the needle which was withdrawn, keeping less than 3 cm of catheter in the peribulbar space. In contrast with previously described techniques,[4–6] we avoided an upward and medial direction of the Tuohy needle which may result in retrobulbar placement with an increased risk of optic nerve injury, globe perforation and haemorrhage or, because of a possible retrobulbar position of the catheter after withdrawal of the needle, may be accompanied by serious central nervous system complications at the time of drug administration.[2]

Continuous decompression was then performed until surgery started. The catheter was taped to the cheek with plaster. During surgery, patients received a 5-ml bolus of 2% lignocaine via the catheter at each complaint of pain. After negative test aspiration, each injection was made slowly, over 2 min, to avoid significant increased pressure in the operating field. Injection was discontinued if the surgeon requested it, to be completed later. During the entire procedure, we monitored continuously heart rate and pulse oxygen saturation. Arterial pressure was measured by automated sphygmomanometry. After leaving the operating theatre, patients were asked to evaluate the quality of anaesthesia using a five-point scale.

Mean age and weight of the patients were 64 (range 16–89) yr and 66 (SD 13) kg, respectively. Time of decompression was 32 (SD 11) min. A catheter was used for prolonging anaesthesia in 92 patients, most often for one injection (58 cases). Three patients required up to four injections of lignocaine, thus receiving a maximum dose of 560 mg, including the initial block. The time for the first request from the initial peribulbar block was 52 (15) min, with wide inter-individual variability (range 25–95 min). Surgery included 28 cases of vitrectomy (duration 43 (range 15–80) min), 121 cases of retinal detachment (duration 56 (10–120) min) and 68 cases of retinal peeling (duration 33 (15–60) min). Use of the catheter was, respectively, 54%, 52% and 20%.

## Comment

Verbal contact was maintained in all patients. Neither additional sedation nor general anaesthesia was required. Intraoperative injection of lignocaine 5 ml was compatible with continuation of surgery and did not inconvenience the surgeon. With the exception of one patient who declared that the operation was unpleasant, there were no bad or medium responses when we asked patients to evaluate anaesthesia. No local complications were observed, except two cases of lower eyelid haematoma which resolved spontaneously. No symptoms of local anaesthetic toxicity were observed. One episode of reflex bradycardia (heart rate less than 40 beat $\text{min}^{-1}$) was observed in a 40-yr-old patient who had received three injections of lignocaine for inadequate analgesia. With the exception of this case, there were no changes in heart rate, arterial pressure or pulse oxygen saturation during surgery.

We conclude that catheter insertion into the peribulbar space is an easy and reliable method of performing a greater variety of ophthalmic surgery with regional anaesthesia.

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# Continuous brachial plexus infusion of butorphanol–mepivacaine mixtures for analgesia after upper extremity surgery

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## Summary

We have recently reported that continuous administration of butorphanol into the brachial plexus neurovascular sheath provided superior analgesia compared with that obtained with continuous i.v. administration. Furthermore, we found that analgesia was most pronounced when a mixture of mepivacaine and butorphanol was given and that butorphanol alone ranked next. In this study, we increased the dose of butorphanol, compared with that used in our previous reports, and an initial bolus dose of butorphanol was administered into the brachial plexus neurovascular sheath just after surgery had ended. Thereafter, postoperative pain relief was estimated. In patients undergoing upper extremity surgery with continuous axillary brachial plexus block, group A received a bolus of 1 ml of physiological saline with 1.5% mepivacaine, 10 ml into the brachial plexus sheath followed by a continuous brachial plexus infusion of 0.5% mepivacaine with butorphanol 6 mg at a rate of 144 ml/72 h. Group B was given a bolus of butorphanol 1 mg (1 ml) with 1.5% mepivacaine, 10 ml into the brachial plexus sheath and a continuous brachial plexus infusion of 0.5% mepivacaine with butorphanol 6 mg at a rate of 144 ml/72 h. After operation, VAS scores did not differ between the two groups. The time to first use of supplementary analgesia did not differ significantly between the groups and there were no significant differences in the number of patients who required supplementary analgesia. These results indicate that continuous butorphanol 2 mg day$^{-1}$ with 0.5% mepivacaine provided sufficient postoperative analgesia after upper limb surgery. (*Br. J. Anaesth.* 1997; **78**: 83–85)

**Key words**
Analgesia, postoperative. Analgesic techniques, regional, brachial plexus. Analgesics opioid, butorphanol. Anaesthetics local, mepivacaine.

We reported recently that administration of analgesics into the brachial plexus neurovascular sheath produced good postoperative analgesia after upper limb surgery[1 2]: we showed that continuous administration of butorphanol into the brachial plexus neurovascular sheath provided superior analgesia compared with that achieved with continuous systemic i.v. injection after upper extremity surgery.[1] Furthermore, we compared postoperative pain relief produced by continuous infusion of three types of solution into the axillary sheath (butorphanol alone, mepivacaine alone or a mixture of mepivacaine and butorphanol) and found that analgesia was most pronounced with a mixture of mepivacaine and butorphanol and that butorphanol alone ranked next.[2] We proposed that it might be possible to potentiate postoperative pain relief by increasing the concentration of local anaesthetic, increasing the rate of administration of local anaesthetic or increasing the dose of opioid.[2] In this study, we increased the dose of butorphanol, compared with our previous reports,[2] and estimated postoperative pain relief after initial bolus administration of butorphanol into the brachial plexus neurovascular sheath just after surgery had ended.

## Methods and results

With the approval of our institutional Ethics Committee and written informed consent, we studied 25 patients undergoing elective upper extremity surgery. All patients were ASA I or II, aged 13–82 yr. Similar surgical procedures were performed in both groups. Surgery was performed by the same orthopaedic surgeon. Patients received oral roxatidine acetate hydrochloride ($H_2$ antagonist) 75 mg, on the night before surgery and 2 h before entering the operating room.

During surgery, patients were given a continuous axillary brachial plexus block by i.v. administration of 30 ml of 1.5% mepivacaine after repeated aspiration tests. The block was performed as previously.[1 2] All blocks were performed by the same anaesthetist.

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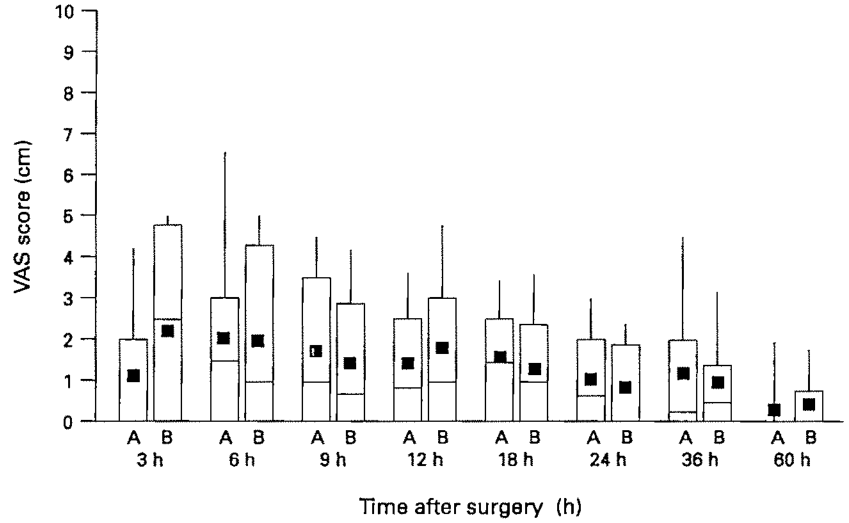

*Figure 1* Postoperative visual analogue scale (VAS) scores in groups A and B. Lower and upper borders of the box=25th to 75th percentiles; horizontal line within the box=median, marking the 50th percentile; rectangular symbols in the box=mean; and error bars=90th percentile.

*Table 1* Number of patients requiring supplementary analgesia and those showing side effects after surgery. No significant differences between the groups

| | Group A ($n$=14) | Group B ($n$=11) |
|---|---|---|
| Required supplementary analgesia | 5 | 4 |
| Nausea | 3 | 5 |
| Vomiting | 2 | 4 |
| Slight drowsiness | 3 | 4 |
| Dizziness | 1 | 2 |

Surgery was started after complete analgesia was obtained in the surgical field. Mepivacaine 1.5% (10 ml) was given every 90 min. Sedation was provided by midazolam i.v. at the discretion of the anaesthetist. Patients were excluded from the study when complete analgesia in the surgical area was not achieved with the initial block.

Immediately after surgery had ended, patients were allocated randomly, in a double-blind design, to one of two groups. Group A received a bolus of 1 ml of physiological saline with 1.5% mepivacaine, 10 ml into the brachial plexus sheath followed by continuous brachial plexus infusion of 0.5% mepivacaine with butorphanol 6 mg at a rate of 144 ml/72 h using a disposable-type continuous microinfuser (Infusor LV2ml/hr, Baxter Healthcare Corporation, Deerfield, IL, USA). The solution consisted of 1% mepivacaine 72 ml, physiological saline 66 ml and butorphanol 6 ml (6 mg). Group B was given a bolus of butorphanol 1 mg (1 ml) with 1.5% mepivacaine, 10 ml into the brachial plexus sheath followed by continuous brachial plexus infusion of 0.5% mepivacaine with butorphanol 6 mg at a rate of 144 ml/72 h.

Diclofenac sodium suppository was available for supplementary analgesia to establish comfort at rest; this was administered as a single 50-mg dose. No other opioids or sedatives were administered.

Patients rated pain at rest on 10-cm unmarked linear visual analogue scales, ranging from "no pain" to "unbearable pain". Scores were recorded at 3, 6, 9, 12, 18, 24, 36 and 60 h after surgery. The time and dose of supplementary analgesic medication were recorded.

There were 14 patients assigned to group A and 11 to group B. There were no significant differences between the two groups in sex distribution, age, weight, height, dose of 1.5% mepivacaine or duration of surgery (Fisher's exact probability tests, unpaired $t$ test and Mann–Whitney $U$ test).

Postoperative VAS scores did not differ between the two groups (fig. 1).

The time to first use of supplementary analgesia (diclofenac sodium suppository) did not differ significantly between the two groups using survival analysis (generalized Wilcoxon test and Cox–Mantel test), and there were no significant differences between the groups in the numbers of patients who required supplementary analgesia (table 1). There were no significant differences in the incidence of side effects between the two groups (table 1).

## Comment

Extradural analgesia with combinations of local anaesthetics and opioids is commonly used for postoperative pain relief[3] and initial bolus administration of opioid or local anaesthetic, or both, is generally conducted before continuous infusion of analgesics.[4] In our recent report,[2] we suggested that postoperative pain relief might be potentiated by increasing the concentration of local anaesthetic, increasing the rate of administration of local anaesthetic or increasing the dose of opioid. In this study, we increased the dose of butorphanol, compared with that used previously,[2] by administering an initial bolus dose of butorphanol into the brachial plexus sheath just after surgery had ended. Thereafter, postoperative pain relief was estimated.

There were no significant differences between the groups in VAS scores, time to first use of supplementary analgesia and number of patients who required supplementary analgesia, implying that continuous butorphanol 2 mg day$^{-1}$ was sufficient for postoperative analgesia after upper limb surgery. The reason for the lack of difference between the two groups in postoperative pain scores was that both pain relief methods were probably adequate for postoperative pain relief from the early postoperative period. To potentiate postoperative pain relief, we recommend increasing the concentration of local anaesthetic or increasing the rate of administration of local anaesthetic, especially during the early postoperative period.

Peripherally acting opioids[5 6] are likely to be useful clinically because the reduction in adverse effects by the use of low-dose opioids would be advantageous, but further investigation is needed.

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# Validation of pulse oximetry for monitoring of hypoxaemic episodes in the late postoperative period

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## Summary

We monitored 12 patients undergoing major abdominal surgery using a pulse oximeter (Nellcor N-200) and a transcutaneous oxygen tension monitor (TINA, Radiometer A/S) on the second or third night after operation. Of the shortest hypoxaemic episodes measured with the pulse oximeter ($\leq$30 s duration), 78% also occurred in the transcutaneous oxygen tension measurement. Episodes of longer duration ($\geq$1 min duration on the pulse oximeter) were, in 95% of cases, reflected in the transcutaneous oxygen tension measurement also. Thus postoperative episodic desaturations lasting $\geq$1 min are at least 95% likely to be a real phenomenon. (*Br. J. Anaesth.* 1997; **78**: 86–87)

**Key words**
Oxygen, inspired concentration. Oxygen saturation. Hypoxaemia. Measurement techniques, oximeters. Surgery, postoperative period.

Late postoperative episodic hypoxaemia is frequent during the second to fourth nights after major surgery, and may be related to development of cardiac complications.[1] Postoperative episodic hypoxaemia has been verified previously by pulse oximetry. However, it is possible that some of the hypoxaemic episodes may have been motion artefacts rather than hypoxaemic events.[2] Measurement of transcutaneous oxygen tension using a heated Clark electrode is not sensitive to motion,[3] and this method is therefore a suitable reference for validating pulse oximetry monitoring of episodic hypoxaemia.[4]

The aim of the study was to validate pulse oximetry for monitoring of episodic hypoxaemia after major surgery by simultaneous and continuous monitoring of transcutaneous oxygen tension ($Tc_{O_2}$) and transcutaneous oxygen saturation ($Sp_{O_2}$).

## Methods and results

We studied 12 patients (six men, median age 66 (range 44–84) yr, weight 70 (55–85) kg, height 170 (160–180) cm) in the ward after major abdominal surgery. Patients were studied on the second or third night after laparotomy during the hours of 23:00–07:00. Eight patients underwent colonic resection, two gastric procedures and two operations for adhesions. The anaesthetic technique was inhalation (enflurane, 11 patients) or i.v. (midazolam/low-dose fentanyl, one patient). Nine of the patients received additional extradural anaesthesia during operation. Supplementary oxygen therapy was not given during the study night. In nine patients postoperative pain therapy was performed with continuous extradural infusion of bupivacaine 10 mg $h^{-1}$ and morphine 4.8 mg $day^{-1}$, and in three patients postoperative pain was treated with morphine i.m. on demand.

Arterial oxygen saturation ($Sp_{O_2}$) was measured continuously with a Nellcor N-200 pulse oximeter (Nellcor Inc., Pleasanton, CA, USA) using an adhesive finger probe, and transcutaneous oxygen tension ($Tc_{O_2}$) was measured with a TINA transcutaneous oxygen tension monitor (Radiometer A/S, Copenhagen, Denmark). The $Tc_{O_2}$ electrode was heated to 43 °C and placed distally at the volar side of the same arm as the $Sp_{O_2}$ probe. Data for $Sp_{O_2}$ and $Tc_{O_2}$ were printed simultaneously at bedside on an analogue recorder.

An episodic hypoxaemic event in the $Sp_{O_2}$ tracing was defined as a sudden reduction in $Sp_{O_2}$ of $\geq$5% from baseline and occurring within 2 min.[1] In the $Tc_{O_2}$ tracing a hypoxaemic event was defined as a sudden reduction in $Tc_{O_2}$ of more than 0.3 kPa and occurring within 2 min. Events were considered to be coherent if the $Tc_{O_2}$ event was delayed by not more than 30 s from the $Sp_{O_2}$ event.

The study was approved by the local Ethics Committee and all patients gave written informed consent. Group data are given as median (range). For statistical analyses we used Fisher's exact test. $P<0.05$ was considered statistically significant.

Duration of surgery was 175 (75–290) min. For the group of 12 patients, median $Sp_{O_2}$ was 93 (91–96) % and $Tc_{O_2}$ was 4.3 (3.8–5.9) kPa. A total of 481 hypoxaemic episodes were recorded on the pulse oximeter (table 1), of which 424 (88%) episodes were transmitted to the $Tc_{O_2}$ tracing. There were no instances of episodes in the $Tc_{O_2}$ curve not reflected in the $Sp_{O_2}$ curve; 95% of the hypoxaemic

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*Table 1* Occurrence of late postoperative hypoxaemic episodes assessed by pulse oximetry and transcutaneous measurement ($Tc_{O_2}$) in relation to duration of the desaturation episode

| Duration of episode in pulse oximetry measurement | Total No. of episodes | Reflected in $Tc_{O_2}$ (no. of episodes) | Not reflected in $Tc_{O_2}$ (no. of episodes) | *P* (Fisher's test) |
|---|---|---|---|---|
| <30 s | 30 | 7 (23%) | 23 (77%) | =0.0001 |
| 30 s | 161 | 142 (88%) | 19 (12%) | <0.00005 |
| Total <1 min | 191 | 149 (78%) | 42 (22%) | <0.00005 |
| 1 min | 195 | 183 (94%) | 12 (6%) | <0.00005 |
| 1 min 30 s | 46 | 44 (96%) | 2 (4%) | <0.00005 |
| 2 min | 13 | 13 (100%) | 0 (0%) | <0.00005 |
| >2 min | 36 | 35 (97%) | 1 (3%) | <0.00005 |
| Total≥1 min | 290 | 275 (95%) | 15 (5%) | <0.00005 |
| Total No. of episodes | 481 | 424 (88%) | 57 (12%) | <0.00005 |

episodes lasting ≥1 min also occurred on the $Tc_{O_2}$ curve, whereas 5% did not (difference between rates=90%, 95% confidence limits of difference between rates=78–101%).

## Comment

The principal finding of our study was that episodic oxygen desaturations were reflected in transcutaneous oxygen tension measurements in 95% of cases if the episodes lasted 1 min or more. It is presumed that if a hypoxaemic episode occurs in both $Sp_{O_2}$ and $Tc_{O_2}$ tracings it is "real", and if it occurs only in the $Sp_{O_2}$ curve it may (or may not) be an artefact. Thus at least 95% of episodes lasting ≥1 min were real.

Pulse oximetry needs arterial pulsation to measure oxygen saturation. Thus in circumstances when decreased pulsation occurs, for example hypothermia, hypotension and vasoconstriction decrease the ability of the oximeter to measure arterial oxygen saturation. It is not likely, however, that this was the case for the shorter lasting episodes in this study. Movement artefacts may be a significant source of error in pulse oximetry measurements.[2] A previous study evaluating four oximeters in an experimental setting with vibration found no false hypoxaemic episodes with the Nellcor N-200 oximeter (when the $Sp_{O_2}$ signal was read in conjunction with the ECG signal for data verification) whereas the Ohmeda 3700, the Simed S100 and the Datex Satlite Plus reported spurious hypoxaemic episodes, that is movement artefacts.[2]

The relationship between transcutaneous and arterial oxygen tension depends on skin temperature, skin thickness, chosen place for measurement and correct preparation of the skin.[5] Measurement of transcutaneous oxygen tension, however, is not dependent on motion.[3] In adults, values for transcutaneous oxygen tension are normally much lower than arterial values.[3] Thus in our study the median $Tc_{O_2}$ was only 4.3 kPa. This method is therefore not suitable for measuring exact values for arterial oxygen tension, but sudden changes in arterial oxygen tension are reflected in transcutaneous measurements.[3 4] However, there is the question of response time for the $Tc_{O_2}$ technique. Previous studies have found that with acute changes in arterial oxygen tension, the $Tc_{O_2}$ signal may be dampened or delayed because of the time for transport of oxygen through the skin.[5] Based on various assumptions and the results of earlier experimental studies, this transport time has been estimated to be in the order of 30 s.[5] In our study, when examining the actual curves for $Sp_{O_2}$ and $Tc_{O_2}$, changes resembled more of an "all or nothing" phenomenon; either the $Sp_{O_2}$ event was reflected almost simultaneously in the $Tc_{O_2}$ curve or the $Sp_{O_2}$ event did not occur. Our limit of 30 s between the $Sp_{O_2}$ and $Tc_{O_2}$ events was arbitrary, as no episodes were reflected in the $Tc_{O_2}$ curve with a delay of more than 30 s. It is therefore more likely that the discrepancy between some of the shortest $Sp_{O_2}$ events and the $Tc_{O_2}$ tracing was caused by motion artefacts (thus an error in the $Sp_{O_2}$ measurement), rather than the $Tc_{O_2}$ not reporting actual hypoxaemic events.

In summary, $Sp_{O_2}$ desaturations lasting ≥1 min, assessed using pulse oximetry in the late postoperative period, represented, with at least 95% certainty, an actual hypoxaemic episode. Short-lasting (≤30 s) episodic hypoxaemia, as assessed by pulse oximetry, may in 22% of instances or less, not reflect an actual hypoxaemic event.

## Acknowledgements

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# Spinal anaesthesia inhibits central temporal summation

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## Summary

In a previous investigation we found that extradural anaesthesia did not adequately inhibit temporal summation of repeated electrical stimuli: pain to repeated stimuli was blocked in only one of 10 patients, and pain thresholds to repeated stimuli were significantly lower than pain thresholds to a single stimulus. In this study we have investigated in 10 patients the effect of spinal anaesthesia on temporal summation, assessed by repeated electrical stimulation of the sural nerve. Plain 0.5% bupivacaine 18 mg was injected at L2–3. The pain threshold to a single electrical stimulus, summation threshold (increase in perception during repeated electrical stimuli with five impulses of the same intensity at 2 Hz), pinprick and cold sensation were assessed. After spinal anaesthesia, pain to both single and repeated stimulation, and pinprick and cold sensation, disappeared in all patients. We conclude that spinal anaesthesia inhibits temporal summation elicited by repeated electrical stimulation. (*Br. J. Anaesth.* 1997; **78**: 88–89)

**Key words**
Anaesthetic techniques, subarachnoid. Pain, experimental. Pain, threshold.

Repetition of a peripheral stimulus can cause increased pain perception (temporal summation). Increased and prolonged firing of dorsal horn neurones after repeated stimulation[1] (central sensitization) is probably the mechanism explaining temporal summation.

Repeated cutaneous stimulation can be used to investigate temporal summation in humans.[2] Nociceptive reflex and subjective pain thresholds after repeated stimulation have been found to be increased slightly by isoflurane concentrations used for surgical analgesia,[3] ketamine[4] and alfentanil,[5] although none of these drugs adequately blocked temporal summation. In a previous investigation,[6] we found that even extradural anaesthesia did not completely block temporal summation of repeated electrical stimuli: pain to repeated stimuli was blocked in only one of 10 patients, and pain thresholds to repeated stimuli were significantly lower than pain thresholds to a single stimulus.

The aim of this study was to assess the effect of spinal anaesthesia on temporal summation, assessed by repeated electrical stimulation.

## Methods and results

We studied 10 ASA I–II patients (five male), median age 43 (range 18–54) yr, median body weight 71 (54–85) kg and median height 170 (157–182) cm, undergoing spinal anaesthesia for elective surgery. Exclusion criteria were: age less than 18 or more than 65 yr, heart disease, pregnancy, opioid intake during the last 2 weeks, intake of other analgesics during the last 24 h, alcohol abuse and use of psychotropic drugs. The study was approved by the local Ethics Committee and informed consent was obtained from all patients.

Patients were not premedicated. Spinal anaesthesia was performed in the sitting position, at L2–3, with a 27-gauge Quincke needle, by the midline approach. Plain 0.5% bupivacaine 18 mg was injected over 40–45 s, with the bevel of the needle pointing cranially. Cerebrospinal fluid (0.2 ml) was aspirated and re-injected after administering half and the whole dose, to assure intrathecal placement of the needle. After injection patients were placed in the supine horizontal position.

Bipolar surface silver–silver chloride electrodes were placed behind the lateral malleolus for stimulation of the sural nerve. A 25-ms, train-of-five, 1-ms, square-wave impulse (perceived as a single stimulus) was delivered from a computer-controlled constant current stimulator (University of Aalborg, Denmark). To determine the single stimulus pain threshold, current intensity was increased from 2 mA in steps of 1–5 mA until pain was evoked, or a maximum current of 60 mA was reached. In the last case, the threshold was defined as 60 mA. The mean of two threshold measurements was calculated. To determine the threshold for temporal summation, the single stimulus was repeated five times at 2 Hz.[2] Current intensity was increased as described above until summation (increase in perception during the five stimuli) was observed, or a maximum current of 60 mA was reached. In the last case, the threshold

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*Table 1* Median values (ranges) of thresholds to single (pain threshold) and repeated (increasing perception during five stimulations at 2 Hz) electrical stimulation of the sural nerve. Number of patients displaying slight or normal perception of pinprick and cold at the site of electrical stimulation

| | Basal | 10 min | 20 min | 30 min | 40 min |
|---|---|---|---|---|---|
| Single stimulus threshold (mA) | 7 (2–12) | 60 (19–60) | 60 (39–60) | 60 (60–60) | 60 (60–60) |
| Repeated stimuli threshold (mA) | 4 (1–7) | 53 (10–60) | 60 (35–60) | 60 (40–60) | 60 (60–60) |
| Pinprick sensation (No. patients) | 10 | 1 | 0 | 0 | 0 |
| Cold (No. patients) | 10 | 0 | 0 | 0 | 0 |

was defined as 60 mA. The mean of two threshold measurements was calculated.

Sensitivity to pinprick and cold were tested 2 cm anterior to the site of electrical stimulation (dermatome S1) and on the forehead to allow comparison with a non-anaesthetized area. Pinprick was performed with a 21-gauge sharp-bevelled needle, and cold test with gel bags (Physiopack, Fisch Laboratories) kept in a freezer, applied to 4 cm$^2$ of skin surface for 2 s. Tests were considered positive when patients reported normal or light perception of puncture or cold compared with sensation at the forehead.

Before spinal puncture a test series (single and repeated stimulations of the sural nerve, pinprick and cold) was performed for training, followed by baseline recordings. The test series was then repeated 10, 20, 30 and 40 min after spinal injection. The upper and lower levels of sensory block were determined 40 min after injection by absence of pinprick sensation. At the end of the experiment patients were transported to the operating room for surgery.

The median upper level of sensory block, as assessed by pinprick, was T9 (range T3–L4). Block of S5 was achieved in every patient.

Each test series lasted 2–4 min. After anaesthesia all patients had single stimulus and summation thresholds more than 60 mA (table 1). Pain to repeated stimulation disappeared in all patients. All patients lost both pinprick and cold sensation.

## Comment

We have shown that spinal anaesthesia effectively blocked pain elicited by single and repeated electrical stimulations of the sural nerve. Pain could not be evoked in any of the 10 patients by repeated stimulation with a maximum current intensity of 60 mA. This contrasts our previous study,[6] where extradural anaesthesia blocked pain to repeated stimulations in only one of 10 patients.

Pinprick and cold sensation disappeared very rapidly after spinal anaesthesia, when pain could still be evoked by electrical stimulation (table 1). This confirms that pinprick and cold tests inadequately assess the efficacy of regional block.[6]

We conclude that spinal anaesthesia inhibits temporal summation of nociceptive stimuli elicited by repeated stimulation of the sural nerve. This indicates that spinal anaesthesia can prevent sensitization of dorsal horn neurones during nociceptive stimulation and could be useful for the prevention of hyperalgesic states.

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# Neuromuscular effects of rocuronium in patients receiving beta-adrenoreceptor blocking, calcium entry blocking and anticonvulsant drugs

P. B. LOAN, F. M. CONNOLLY, R. K. MIRAKHUR, N. KUMAR AND P. FARLING

## Summary

We have studied the onset and duration of action of rocuronium 0.6 mg $kg^{-1}$ in patients receiving therapy for more than 1 month with beta-receptor blocking drugs ($n=16$), calcium entry blocking drugs ($n=17$) or anticonvulsant drugs ($n=14$) and compared these data with those from a control group ($n=27$). Anaesthesia comprised fentanyl, propofol infusion and nitrous oxide in oxygen. Neuromuscular block was monitored by measuring the force of contraction of the adductor pollicis muscle in response to train-of-four (TOF) stimulation. There were no significant differences in onset times between the four groups (mean 62–76 s). Mean times to 25% recovery of T1 (first response in the TOF) and of the TOF ratio of 0.7 were 38 (SD 15) and 58 (22) min, 36 (8) and 61 (19) min, 40 (11) and 68 (22) min, and 25 (6) and 35 (9) min in the control, beta-blocker, calcium entry blocker and anticonvulsant groups, respectively ($P<0.01$ between the anticonvulsant and other groups). We conclude that chronic therapy with anticonvulsant drugs reduces the duration of action of rocuronium. (*Br. J. Anaesth.* 1997; **78**: 90–91)

**Key words**
Neuromuscular block, rocuronium. Interactions (drug). Sympathetic nervous system, adrenergic block. Calcium channel block. Anticonvulsants

Rocuronium is a new non-depolarizing neuromuscular blocking agent with an intermediate duration of action, but with a rapid onset of action.[1] Previous experimental or clinical studies have shown significant alterations in the effects of neuromuscular blocking agents by anticonvulsant, beta-receptor antagonist and calcium channel blocking drugs or in those receiving chronic therapy with these agents.[2–4] Knowledge of these interactions may be important to enable the anaesthetist to avoid delays and risk to the patient from over-curarization, or to anticipate the need for more frequent dosing. The aim of this study was to investigate any clinically important effects of therapy with these three commonly prescribed groups of drugs on the onset and duration of action of rocuronium.

## Methods and results

We studied 74 ASA I–III patients, aged 18–74 yr, with their written informed consent and approval of the Research Ethics Committee. Sixteen patients were receiving chronic therapy (for at least 1 month) with beta-receptor blocking drugs (propranolol and atenolol five each, metoprolol and bisoprolol two each, oxprenolol and celiprolol one each), 17 with calcium entry blocking drugs (nifedipine 12, diltiazem and nicardipine two each, amlodipine one), and 14 with anticonvulsant drugs (carbamazepine alone or in combination with other anticonvulsants 12, phenytoin one, sodium valproate one). Twenty seven patients in the "control" group were not receiving any of these or any other drugs known to interact with neuromuscular blocking agents.

Patients were premedicated with temazepam 10–20 mg and anaesthetized with fentanyl 1–3 μg $kg^{-1}$, propofol 1–2.5 mg $kg^{-1}$ followed by an infusion of propofol, and 65% nitrous oxide in oxygen. The ulnar nerve was stimulated transcutaneously with supramaximal stimuli of 0.2 ms duration in a train-of-four (TOF) sequence at 2 Hz every 12 s and the resultant force of contraction of the adductor pollicis muscle was measured and recorded using a force transducer and a neuromuscular function analyser (Myograph 2000, Biometer Ltd, Denmark). Hand skin temperature was maintained above 32 °C.

The control responses were stabilized for approximately 10 min before administration of rocuronium 0.6 mg $kg^{-1}$. The times from administration of rocuronium to maximal depression of T1 (onset time) and its recovery to 25, 75 and 90% of control, and of recovery of the TOF ratio to 0.7, were recorded. Patient data were subjected to the Kruskal–Wallis test followed by Dunn's test, if significant differences were observed. Neuromuscular data between the control and each of the study groups were subjected to the Wilcoxon test using the Hochberg–Bonferroni correction. $P<0.05$ was accepted as significant.

The times to onset of maximum block and

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*Table 1* Onset and recovery of neuromuscular block. RI=Recovery index. [a]$n=25$, [b]$n=13$, [c]$n=24$, [d]$n=23$; **significantly different from other groups ($P<0.01$)

| | Control group | β-adrenoreceptor blocking group | Calcium entry blocking group | Anticonvulsant group |
|---|---|---|---|---|
| *n* | 27 | 16 | 17 | 14 |
| Onset (s) | | | | |
| Mean (SD) | 63 (12) | 76 (46) | 73 (30) | 62 (13) |
| Median (range) | 60 (44–90) | 66 (45–242) | 65 (50–180) | 62 (38–85) |
| T1 25% (min) | | | | |
| Mean (SD) | 38 (15)[a] | 36 (8) | 40 (11) | 25 (6)**[b] |
| Median (range) | 37 (18–88) | 35 (23–50) | 41 (19–67) | 25 (16–37) |
| TOF 0.7 (min) | | | | |
| Mean (SD) | 58 (22)[c] | 61 (19) | 68 (22) | 35 (9)**[b] |
| Median (range) | 57 (30–122) | 57 (38–114) | 70 (35–116) | 35 (24–52) |
| RI (min) | | | | |
| Mean (SD) | 15 (9)[d] | 14 (6) | 17 (12) | 9 (3)[b] |
| Median (range) | 12 (4–46) | 13 (5–24) | 16 (6–59) | 9 (4–13) |

recovery are shown in table 1. Onset times did not differ significantly between the groups. All patients attained 100% block. There were no significant differences in the recovery times between the control, beta-receptor blocker and calcium entry blocker groups. However, the times for recovery of T1 to 25% and of the TOF ratio to recover to 0.7 in the anticonvulsant group were significantly shorter compared with the other groups ($P<0.01$). The mean T1 25–75% recovery index of 9 min in this group, although shorter, was not statistically significant at the 5% level ($P=0.06$).

## Comment

We have observed a shorter duration of action of rocuronium in patients receiving anticonvulsant therapy, as is known for many other blockers, compared with other classes of drug which caused no significant interaction. The reasons for this effect may be increased plasma protein binding of the blocker, hepatic enzyme induction or proliferation of acetylcholine receptors on the muscle membrane.[5 6]

Calcium entry blocking drugs, such as verapamil, may have neuromuscular blocking effects and may cause difficulty in antagonism of block.[3 7] However, nifedipine, the drug used by the majority of patients in our study, has been shown not to interact significantly with vecuronium in humans[8] although that does not exclude the possibility of an interaction between rocuronium and verapamil.

Although there is some experimental evidence on the interaction of propranolol with neuromuscular blocking agents, it seems unlikely from our results and absence of previous clinical reports with other blockers that there is any important interaction between beta-receptor blocking and neuromuscular blocking drugs.

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# Low-dose rocuronium improves conditions for tracheal intubation after induction of anaesthesia with propofol and alfentanil†

K. BARCLAY, K. EGGERS AND T. ASAI

## Summary

We studied 60 adult patients to assess if low doses of rocuronium improved conditions for tracheal intubation during induction of anaesthesia with propofol 2.5 mg kg$^{-1}$ and alfentanil 10 μg kg$^{-1}$. In a double-blind, randomized design, patients were allocated to one of three groups: group P=saline; group $R_1$=rocuronium 0.1 mg kg$^{-1}$; and group $R_3$=rocuronium 0.3 mg kg$^{-1}$. Intubation conditions were judged as optimal, suboptimal or failure, based on the scoring of ease of jaw opening and laryngoscopy, position of the vocal cords and degree of straining after tracheal intubation. Intubation conditions were judged as optimal in one patient in group P, in six patients in group $R_1$ and in 18 patients in group $R_3$. Conditions were judged as a failure in seven patients in group P, in one patient in group $R_1$ and in none in group $R_3$. No laryngospasm or other complications were observed in any patient. The addition of low doses of rocuronium significantly improved intubation conditions ($P<<0.001$). Ventilation was controlled during surgery, and in no patient was any problem encountered with antagonism of neuromuscular block with neostigmine. Injection of rocuronium 0.3 mg kg$^{-1}$ ($ED_{95}$) with propofol and alfentanil provided a high proportion of optimal intubation conditions. (*Br. J. Anaesth.* 1997; **78**: 92–94)

**Key words**
Anaesthetics i.v., propofol. Analgesics opioid, alfentanil. Intubation tracheal. Neuromuscular block, rocuronium

Tracheal intubation may be accomplished after concurrent injection of alfentanil and propofol (without a neuromuscular blocking agent),[1] but a relatively high dose of alfentanil (40 μg kg$^{-1}$ or greater), which may not be suitable for minor surgery of short duration, is required to obtain reliably satisfactory conditions.[1]

A low dose of neuromuscular blocking agent partially paralyses the laryngeal adductor muscles.[2] Thus concurrent injection of a low dose of a neuromuscular blocking agent, propofol and alfentanil may improve intubation conditions. In addition, the use of low doses of a neuromuscular blocking agent, in theory, shortens the time for recovery from neuromuscular block and reduces the requirement for anticholinesterase drugs. Rocuronium 0.3 mg kg$^{-1}$ is the $ED_{95}$ at the adductor pollicis muscle (as estimated by supramaximal single twitch stimulation at 0.1 Hz)[3] and the $ED_{50}$ at the laryngeal adductor muscles,[2] and is half the recommended intubating dose.[3]

The aim of this study was to examine if injection of a low dose of rocuronium during induction of anaesthesia with propofol and alfentanil improved intubation conditions.

## Methods and results

In a double-blind, randomized design, we studied 60 patients, aged 18–50 yr, after obtaining local Research Ethics Committee approval and written informed consent from all patients. Patients were excluded if they were obese or at risk of pulmonary aspiration, smoked more than 10 cigarettes per day, their tracheas were known to be difficult to intubate or where coughing or straining after tracheal intubation might be detrimental.

Patients were allocated randomly (in blocks of nine) to one of three groups: group P, placebo (10 ml of 0.9% saline); group $R_1$, rocuronium 0.1 mg kg$^{-1}$ made up to 10 ml with saline; group $R_3$, rocuronium 0.3 mg kg$^{-1}$ made up to 10 ml with saline.

Temazepam 20–30 mg was given orally, 1 h before induction of anaesthesia. The patient's lungs were preoxygenated with 100% oxygen via a face mask for 3 min. Immediately after injection of alfentanil 10 μg kg$^{-1}$, propofol 2.5 mg kg$^{-1}$ containing lignocaine 10 mg was injected. If the patient did not lose consciousness after injection of propofol 2.5 mg kg$^{-1}$, the patient was withdrawn from the study. The study drug was then given and the i.v. cannula flushed with saline 20 ml. Anaesthesia was maintained with 50% nitrous oxide in oxygen and an i.v infusion of propofol 10 mg kg$^{-1}$ h$^{-1}$. The lungs were ventilated manually to maintain normocapnia. Two minutes

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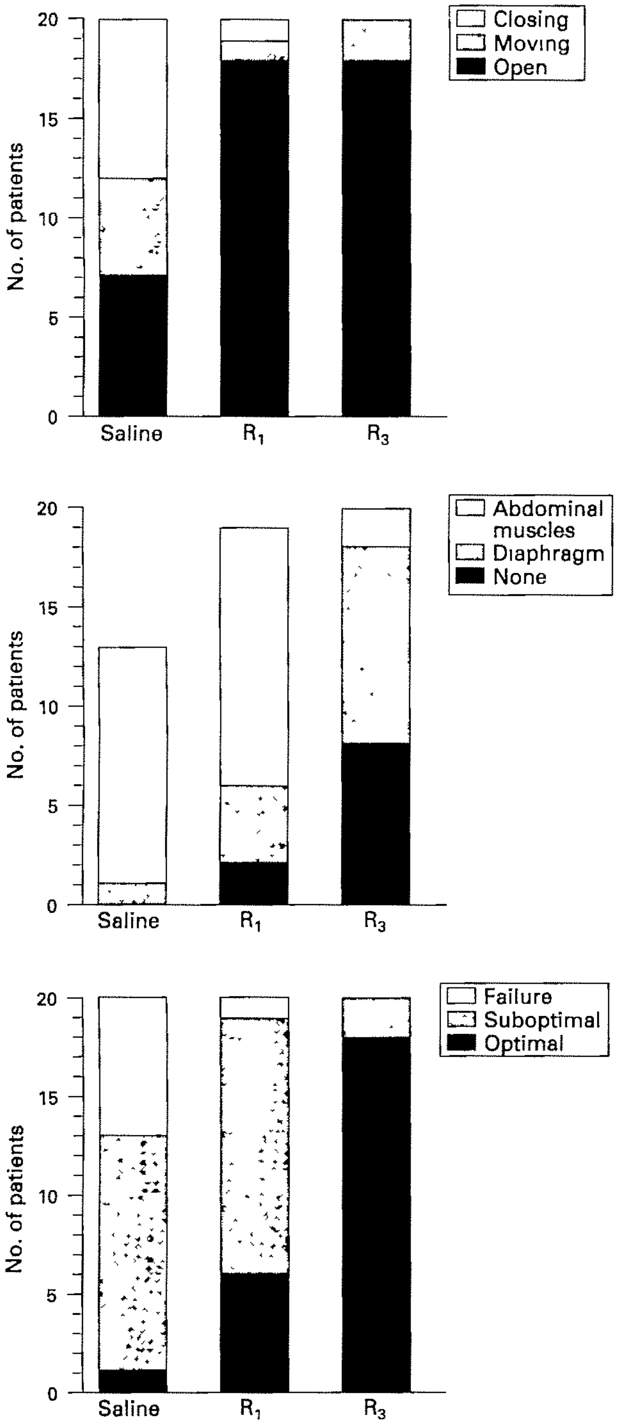

*Figure 1* Position and movement of the vocal cords (top), degree of straining after tracheal intubation (middle) and overall conditions for tracheal intubation (bottom). Saline=no rocuronium, $R_1$=rocuronium 0.1 mg $kg^{-1}$ and $R_3$=rocuronium 0.3 mg $kg^{-1}$. In all groups, propofol 2.5 mg $kg^{-1}$ and alfentanil 10 µg $kg^{-1}$ were given.

after administration of the study drug, an investigator, who was blinded as to the allocation, opened the patient's mouth and attempted to intubate the trachea using a Macintosh laryngoscope. A 9.0-mm id tracheal tube was used in males and a 8.0-mm id tube in females. Tracheal intubation was not attempted if the vocal cords were nearly or fully closed and if there was a possibility of injury to the vocal cords.

The investigator assessed three factors: ease of jaw opening and laryngoscopy (1=easy; 2=fair; 3=difficult), position of the vocal cords and their movement (1=open; 2=moving; 3=closing) and degree of straining ("bucking") after tracheal intubation and cuff inflation (1=none; 2=with diaphragm; 3=with abdominal muscles). The occurrence of any significant complication was recorded.

Overall conditions for tracheal intubation were scored in three grades: optimal, suboptimal and failure. Tracheal intubation was judged as optimal when all scores were 1 or 2, and judged as suboptimal if any of the scores were 3. Failure to intubate was scored as a failure.

Chi-square test for trend was used to compare intubation conditions between group P and groups $R_1$ and $R_3$ (pooled) and if this proved significant, it was used to compare intubation conditions between groups $R_1$ and $R_3$. $P<0.05$ was considered significant. Confidence intervals (CI) for the proportion of optimal intubation conditions in groups $R_1$ and $R_3$ were also calculated.

We expected that intubation conditions would be optimal in 30% of patients in group P and in 80% of patients in group $R_3$.[4] Thus 20 patients in each group would be sufficient to detect a difference of 50% between groups P and $R_3$ with a power of 80–90% at $P$=0.05.

Each group consisted of 20 patients: mean ages in the three groups were similar (27 yr (group P), 30 yr (group $R_1$) and 29 yr (group $R_3$)), but mean weights were different (64 kg (group P), 74 kg (group $R_1$) and 72 kg (group $R_3$)).

Rocuronium 0.1 and 0.3 mg $kg^{-1}$ (pooled) significantly improved intubation conditions ($P<<0.001$) (fig. 1). Intubation conditions were significantly better in group $R_3$ than in group $R_1$ ($P<0.001$). Laryngoscopy was easy in all patients. The proportions of optimal intubation conditions were 30% (95% CI 10–50%) in group $R_1$ and 90% (68–99%) in group $R_3$. In no patient did laryngospasm, bronchospasm, hypoxaemia or other significant complications occur.

## Comment

We have shown that a low dose of rocuronium during induction of anaesthesia with propofol 2.5 mg $kg^{-1}$ and alfentanil 10 µg $kg^{-1}$ improved conditions for tracheal intubation, and that rocuronium 0.3 mg $kg^{-1}$ (half "initial dose") provided optimal conditions in most patients.

The proportion of optimal intubation conditions after administration of propofol 2.5 mg $kg^{-1}$ was greater when the time between injection of propofol and tracheal intubation was short.[5] Therefore, the choice of a neuromuscular blocking agent with a short onset time may be necessary to obtain a high proportion of optimal intubation conditions. Rocuronium 0.25 mg $kg^{-1}$ has an onset time to maximum neuromuscular block of the laryngeal adductor muscles of 1.6 min, which is shorter than that of other non-depolarizing neuromuscular blocking agents currently available.[2 6]

Onset time shortens as the dose of rocuronium increases for doses producing complete neuromuscular block; however, when lower doses which are insufficient to produce complete block are given ($<0.68$ mg $kg^{-1}$, $ED_{90}$ at the laryngeal adductor muscles[2]), onset time is similar, regardless of the dose.[6]

In this study, rocuronium 0.1 mg $kg^{-1}$ appeared to relax the laryngeal adductor muscles; however, rocuronium 0.3 mg $kg^{-1}$ would be required to minimize the incidence of straining after tracheal intubation.

After injection of rocuronium 0.25 mg $kg^{-1}$, maximum neuromuscular block of the adductor pollicis is approximately 70%, and the time to spontaneous 90% recovery of T1 twitch height at this muscle is about 10 min.[2] Therefore, it should be possible to antagonize neuromuscular block immediately after injection of this dose of rocuronium, and the incidence of residual neuromuscular block after surgery is likely to be low. In this study, ventilation was controlled during surgery, and in no patient were there problems with antagonism of neuromuscular block with neostigmine, although we did not study this formally.

## Acknowledgements

We thank Dr M. Harmer, Senior Lecturer, Department of Anaesthetics and Intensive Care Medicine, University of Wales College of Medicine, for his encouragement and supervision of the study. We also thank Organon Teknika for their generous supply of rocuronium.

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*British Journal of Anaesthesia* 1997; 78: 95–96

# Effects of desflurane and isoflurane on splanchnic microcirculation during major surgery

J. O'Riordan, H. A. O'Beirne, Y. Young and M. C. Bellamy

## Summary

Isoflurane has been considered the agent of choice where preservation of splanchnic blood flow is required. Liver blood flow and the hepatic artery buffer response are maintained better in the presence of isoflurane than with other volatile anaesthetic agents. The effects of desflurane have not been assessed in humans. Therefore, we have compared the effects of isoflurane and desflurane anaesthesia on small bowel and hepatic microcirculatory flow during major surgery using laser Doppler flowmetry in a prospective, randomized, single-blind, crossover study. Patients were allocated randomly to receive desflurane or isoflurane (1 MAC) in oxygen-enriched air. Steady-state jejunal and liver blood flow in segment III were assessed by laser Doppler flowmetry. Volatile anaesthetics were then interchanged, and measurements repeated at steady state. Desflurane anaesthesia at 1 MAC was associated with significantly greater gut blood flow than 1 MAC of isoflurane. These differences could not be explained by systemic haemodynamic differences. The similarity in total hepatic flow between groups implies an intact hepatic artery buffer response with desflurane and isoflurane. (*Br. J. Anaesth.* 1997; **78**: 95–96)

**Key words**
Anaesthetics volatile, desflurane. Anaesthetics volatile, isoflurane. Liver, blood flow.

Surgery and anaesthesia are known to compromise hepatic blood flow. Patients with pre-existing hepatic dysfunction have a high morbidity and mortality rate. Liver function is compromised when splanchnic blood flow is reduced; major surgery is associated with a significant increase in serum concentrations of liver enzymes.[1]

Inhalation agents affect splanchnic vascular tone to varying degrees. Increased splanchnic vasodilatation may increase portal venous flow to the liver, as occurs with isoflurane. Isoflurane maintains the hepatic artery buffer response better than other volatile anaesthetic agents.[2] The effects of desflurane on the buffer response and liver blood flow have not been assessed in humans. Therefore, we have compared the effects of isoflurane and desflurane anaesthesia on small bowel and hepatic microcirculatory flow during major surgery in human using laser Doppler flowmetry (LDF). The laser Doppler flowmeter (PF3, Perimed, Jarfalla, Sweden) uses a helium/neon laser (632.8 nm). This light is guided to the measurement site via 1.75 m of optical fibre. Two identical adjacent fibres receive backscattered light from the tissues, which is transmitted to independent photodetectors. This backscattered portion consists of light scattered from the static tissue matrix, which has not been Doppler-shifted, and a spectrally broadened component resulting from interactions with moving red blood cells. Optical mixing of these components at the photodetector surface produces an electrical signal which results in an output voltage. This varies linearly with the product of mean red blood cell velocity and red blood cell concentration.

The laser Doppler produces an arbitrary scale of perfusion units (PU), a deflection of 2.5 V=250 PU, set when calibrating the machine with latex microspheres 2 μm supplied by the manufacturer. While this is generally accepted as a measure of flow in tissue microcirculation, LDF provides an accurate estimation of total liver blood flow in humans.[3]

## Methods and results

After obtaining Ethics Committee approval and informed patient consent for this prospective, randomized single-blind, crossover study, we studied 10 adult patients undergoing elective major upper abdominal surgery. Patients with liver disease were excluded.

After premedication with temazepam 20 mg orally, anaesthesia was induced with thiopentone 3 mg $kg^{-1}$ and fentanyl 3 μg $kg^{-1}$. Neuromuscular block was produced by atracurium 0.5 mg $kg^{-1}$ followed by an infusion of 0.4 mg $kg^{-1}$ $h^{-1}$. Patients were allocated randomly to receive either desflurane or isoflurane (1 MAC) in oxygen-enriched air. (1 MAC was taken as the end-tidal concentration of the volatile agent in oxygen, adjusted for age,

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*Table 1* Laser Doppler flow in the jejunum and liver segment III during desflurane or isoflurane anaesthesia (median (interquartile range))

| | Blood flow (PU) | *P* |
|---|---|---|
| Gut (isoflurane) | 94 (75–154) | 0.02 |
| Gut (desflurane) | 186 (146–262) | |
| Liver (isoflurane) | 137 (58–168) | 0.26 |
| Liver (desflurane) | 175 (54–453) | |

according to our pharmacy data sheets.) Randomization was achieved using pre-sealed envelopes containing instructions for the order of administration of volatile agent. A radial artery cannula and central venous catheter were inserted. Direct pressure readings were measured (Spacelabs Medical 90309, Redmond, WA, USA). Inspired and end-tidal concentrations of volatile agent and end-tidal carbon dioxide concentrations were monitored using Datex modules fitted to an Ohmeda Modulus CD anaesthetic machine (Ohmeda, Madison WI, USA). The lungs were ventilated to maintain normocapnia.

After surgical incision and exposure of the liver, jejunal blood flow and segment III liver blood flow were measured by laser Doppler flowmetry.

All measurements were performed at steady state (inspired/end-tidal concentration <1.1). Volatile agents were then interchanged and measurements repeated when steady state had been produced with the second volatile agent.

Blood flow data were analysed using the paired Wilcoxon signed rank sum test and backward stepwise multiple regression analysis (SPSS for Windows 6.0). Variables included mean arterial pressure, central venous pressure and gut perfusion units. Results are expressed as median (interquartile range). Haemodynamic variables were compared using Wilcoxan's signed rank sum test and expressed as mean (interquartile range). There were no differences in mean arterial pressure (78 (70–89) mm Hg for isoflurane compared with 74 (65–81) mm Hg for desflurane), central venous pressure (8.5 (2–12) mm Hg compared with 8.5 (3–10) mm Hg) or heart rate (82 (70–89) beat $\text{min}^{-1}$ *vs* 83 (62–101) beat $\text{min}^{-1}$) between periods of isoflurane compared with desflurane administration. However, gut blood flow was significantly higher during desflurane than during isoflurane administration. Differences in liver blood flow were much less marked (table 1).

Multiple regression described liver blood flow as (1.3×gut blood flow)−24, $P<0.0001$, $r^2=0.85$.

## Comment

In this study we have used laser Doppler flowmetry (LDF) to measure liver and gut microcirculatory blood flow during major surgery with two different volatile agents in humans. We have shown that during major surgery, desflurane anaesthesia at 1 MAC was associated with significantly greater gut flow than 1 MAC of isoflurane. As there were no systemic haemodynamic differences between the two agents, it is likely that differences in gut blood flow were mediated by a local mechanism.

Liver microcirculatory flow, as measured by LDF in a previous study, correlated well with perfusion pressure.[4] Hepatic perfusion in this study was slightly greater during desflurane than during isoflurane administration, but this was not significant. Increasing portal blood flow tends to reduce hepatic arterial blood flow in the presence of an intact hepatic artery buffer response, thus maintaining near constant total hepatic blood flow. Although a type II error cannot be excluded, the similarity in total hepatic flow between agents implies an intact hepatic artery buffer response with desflurane and isoflurane. This has been shown previously in dogs, but not in humans.[5] The hepatic artery buffer response is a semi-reciprocal autoregulatory mechanism whereby changes in portal flow inversely affect hepatic arterial flow. This is mediated at the level of the hepatic arteriole and is thought to be a non-neuronal, adenosine-dependent process.[2]

Multiple regression analysis indicated that gut blood flow accounted for 85% of the variability in liver blood flow. This suggests that liver blood flow in this model was largely portal in origin.

Any technique which preserves gut and liver blood flow may reduce morbidity and mortality.[6] These results indicate that desflurane may be beneficial, particularly in high-risk patients.

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# Effect of low-dose dopamine on serum concentrations of prolactin in critically ill patients

A. R. BAILEY AND K. R. BURCHETT

## Summary

Dopamine is a naturally occurring catecholamine with actions in the central nervous system and endocrine systems, including inhibition of prolactin release from the pituitary gland. Prolactin secretion has been shown to be increased in response to physiological stress, while hypoprolactinaemia is associated with a reduction in the cellular immune response. We have investigated the effects of low-dose infusion of dopamine 2.5 $\mu g\ kg^{-1}\ min^{-1}$ on serum concentrations of prolactin in critically ill patients. Six hours after commencing the dopamine infusion, mean serum prolactin concentration had decreased from 746.95 to 128.9 mu. $litre^{-1}$ (normal range 84–488 mu. $litre^{-1}$). This represented a mean reduction of 79.2%, with 35% of patients exhibiting a subnormal concentration while receiving dopamine. This reduction was reversed after cessation of dopamine and reproducible on re-institution. This suppression of the release of dopamine may be a detrimental side effect of low-dose dopamine infusion in critically ill patients. (*Br. J. Anaesth.* 1997; **78**: 97–99)

**Key words**
Sympathetic nervous system, dopamine. Pharmacology, dopamine. Hormones, prolactin. Intensive care.

Dopamine is a naturally occurring catecholamine, the immediate precursor of noradrenaline, which acts as a neurotransmitter in the central nervous system and is also secreted by the adrenal medulla. In addition, dopamine has effects on the hypophyseal–pituitary axis, being involved in the regulation of release of prolactin, growth hormone and thyroid stimulating hormone.

Dopamine acts on $\beta_1$, and to a lesser extent $\beta_2$, adrenergic receptors, $\alpha$ receptors and dopaminergic DA1 and DA2 receptors. Hence dopamine has inotropic, chronotropic and vasoconstrictor properties via adrenergic receptors, while by activation of DA1 receptors, dopamine can produce renal and splanchnic vasodilatation. These effects are dose-dependent, with dopaminergic effects predominating at low dose (0.5–3.0 $\mu g\ kg^{-1}\ min^{-1}$).[1]

Low-dose dopamine is used commonly for its renal vasodilating property in critically ill patient, to maintain renal blood flow, glomerular filtration rate and urine output. However, there is no evidence that incipient renal failure can be aborted, or outcome modified, while arrhythmia, myocardial ischaemia, depression of respiratory drive, increased intrapulmonary shunting and digital necrosis have been reported as side effects of dopamine.[2] Therefore, the continued use of dopamine to "protect" the kidneys must be viewed critically.

The release of prolactin from the pituitary gland is regulated by both the reproductive hormones and central nervous system amines, including dopamine, acting via DA2 receptors on lactograph cells. Stress, surgery and a variety of anaesthetic drugs, including opioids, also increase serum concentrations of prolactin.[3]

Prolactin has been shown to be an immunoregulatory hormone, and hypoprolactinaemia may compromise cellular immune function. In mice, dopamine agonists suppress T-cell-dependent induction of macrophage tumour killing activity and lymphocyte proliferation, while co-administration of prolactin reverses these effects.[4]

Devins and colleagues,[5] using dopamine infusions of $>5\ \mu g\ kg^{-1}\ min^{-1}$, have shown greater than 90% reduction in serum prolactin concentration, with an immediate, but transitory decrease in T-cell response and lymphocyte count. These were reversible after cessation of dopamine. Similarly, data from critically ill infants and children showed that dopamine induced suppression of prolactin release, which is of particular concern as hypoprolactinaemia has been associated with poor clinical outcome in preterm infants through effects on surfactant synthesis, water regulation and gastrointestinal maturation.[6]

The aim of this study was to assess the effect of low "renal" dose dopamine on serum concentrations of prolactin.

## Methods and results

After obtaining local Ethics Committee approval, all adult patients admitted to our intensive care unit

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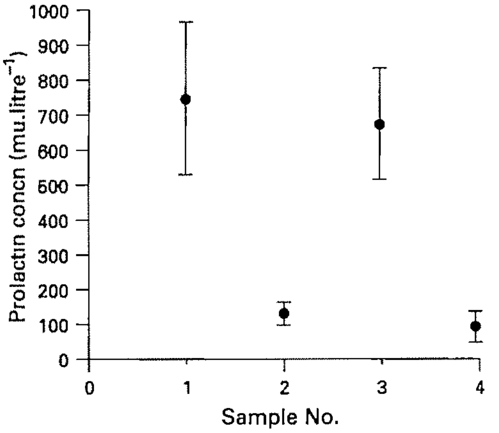

*Figure 1* Changes in mean (95% confidence interval) serum concentrations of prolactin in critically ill patients, after infusion of dopamine 2.5 $\mu$g kg$^{-1}$ min$^{-1}$ Sample 1=baseline serum prolactin concentration, sample 2=after 6 h of infusion of dopamine, sample 3=after a 6-h period without dopamine and sample 4=after another 6 h of dopamine.

(ICU) who were oliguric (<0.5 ml kg$^{-1}$ h$^{-1}$ for more than 2 h) or considered to be at risk of renal impairment because of hypotension (systolic arterial pressure <100 mm Hg), systemic inflammatory response syndrome or after aortic surgery, were considered for entry into the study.

Patients who received dopamine agonist or antagonist drugs before or during the study were excluded and incomplete results from patients who died during the study were not included in the analysis.

After admission to the study, a serum sample was obtained for prolactin assay (sample 1). Dopamine infusion was then commenced at 2.5 $\mu$g kg$^{-1}$ min$^{-1}$ via a central venous catheter, after correction of hypovolaemia with i.v. fluids and treatment of persisting hypotension with non-dopamine inotropes. Standard supportive and specific treatments were implemented as required. After 6 h, serum sample 2 was obtained and dopamine infusion discontinued for another 6 h. After this time serum sample 3 was obtained. Dopamine infusion was then recommenced and the final serum sample (sample 4) was obtained 6 h later. All samples were separated, frozen and analysed in batches for serum prolactin concentration, using an Immulite Prolactin Chemiluminescent Enzyme Immunometric Assay System (Diagnostic Products Corp., LA, USA).

The results were analysed using a paired *t* test.

The study did not involve administration of dopamine to any patient who would not normally have received the drug in their management in our ICU. Any patient who developed oliguria or anuria which did not respond to i.v. fluids, correction of hypotension and i.v. diuretic was recommenced on dopamine infusion and removed from the study.

During the 3-month period, December 1995 to March 1996, 82 patients were admitted to the ICU, of whom 20 (seven female) were included in the study. Age ranged from 16 to 83 yr (mean 60.3 yr) and patients had a median APACHE II score of 18.5 (range 10–24). Two other patients died within 18 h of admission to the study and their results were excluded.

Mean serum prolactin concentration was 746.95 mu. litre$^{-1}$ (95% confidence interval 532–962 mu. litre$^{-1}$) before commencement of dopamine, with 60% of patients having a supranormal level (normal range 84–488 mu. litre$^{-1}$). After 6 h of dopamine infusion, there was a reduction in serum prolactin concentration in all patients by a mean of 79.2 (SD 12.5) % (fig. 1). At this time, 35% of patients exhibited a subnormal serum prolactin concentration. However, this reduction was reversed after cessation of the dopamine infusion for 6 h, with an increase to supranormal levels in 70% of patients. After another 6 h of low-dose dopamine, mean serum concentration of prolactin decreased again, by 83.9 (10.3) %, with 50% of patients exhibiting concentrations less than the normal range.

Measured changes in serum prolactin concentration were all statistically significant at the $P<0.001$ level.

## Comment

The results of this study demonstrate that low-(renal) dose dopamine (2.5 $\mu$g kg$^{-1}$ min$^{-1}$) markedly reduced serum concentrations of prolactin. This effect was both reversible after cessation of dopamine and reproducible after its recommencement. These findings are in accordance with those of other workers[5 6] who used twice the rate of infusion used in this study. Indeed, the magnitude of suppression of serum prolactin in our study was almost as great as that found by Devins and colleagues[5] (79–84% compared with greater than 90%), despite using a lower dose.

It is interesting to note that without dopamine, 60–70% of patients exhibited supranormal prolactin concentrations, whereas with dopamine, serum prolactin concentration decreased to normal and even subnormal concentrations. Prolactin is an immunomodulatory hormone involved in the endocrine response to stress and consequently, any suppression of cellular immunity associated with a reduction in serum prolactin would be undesirable and may predispose critically ill patients to infective complications. Therefore, it seems that in the absence of controlled clinical trials confirming the efficacy of low-dose dopamine as a renal protective agent, its continued use for this purpose should be questioned.

## Acknowledgements

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# Coupling of spontaneous ventilation to heart beat during benzodiazepine sedation

D. C. GALLETLY AND P. D. LARSEN

**Summary**

We have examined in eight male volunteers the effect of midazolam sedation on the relationship between timing of spontaneous ventilations and heart beat. On 2 study days, subjects received either midazolam 0.1 mg $kg^{-1}$ or saline placebo while recordings were made of ECG and ventilatory impedance pneumography. We observed in all midazolam-treated subjects clear evidence of synchronous or non-synchronous coupling between ventilation and heart beat. Non-synchronous coupling was seen in two placebo-treated subjects, one of whom had slept during the recording period. We conclude that cardioventilatory coupling is a major determinant of ventilatory timing in sedated subjects. (*Br. J. Anaesth.* 1997; **78**: 100–101)

**Key words**
Hypnotics benzodiazepine, midazolam. Heart, heart rate. Ventilation, spontaneous.

During midazolam sedation in volunteers, we have previously observed phasic coupling of ventilatory amplitude with slow oscillations (approximately 0.02 Hz) in arterial pressure, heart rate and digital plethysmography.[1] We postulated that linking of cardiorespiratory periodicities might be a result of coupling between regulatory centres within the brain stem. In this study we examined further the effect of midazolam on the relationship between ventilation and heart rate. Specifically, we examined the effect of the benzodiazepine on synchronization between heart beat and ventilation.

## Methods and results

After obtaining Ethics Committee approval and informed consent, we studied eight healthy fasting male volunteers, mean age 22 (range 20–27) yr and mean weight 71 (67–79) kg. On 2 study days, supine subjects breathed oxygen 5 litre $min^{-1}$ from a Hudson mask. ECG (CM5) and ventilation (impedance pneumograph, Corometrics Neo-Trak 502) were recorded using a Macintosh IIcx computer (16 bit ADC, sampling rate of 500 Hz). Recording began after a 15-min stabilization period. Twenty minutes later subjects received midazolam 0.1 mg $kg^{-1}$ i.v. or an equivalent volume of normal saline. Twenty minutes later, flumazenil 0.5 mg or saline was administered i.v. The order of administration of drug and placebo was randomized to ensure an equal number of subjects received placebo or active drug on the first occasion.

Observation of cardioventilatory synchronization was based on a method described by Kenner, Pessenhofer and Schwaberger.[2] From the stored ECG data, we determined the timing of each R wave. The ventilatory signal was filtered to remove cardiovascular artefacts and the time of the peak of each inspiration was determined. We calculated for each R wave the time interval until the next ventilatory peak (RV interval). The RV interval for consecutive R waves was plotted against time of R wave occurrence. Synchronization of heart rate and ventilation is shown as tight horizontal banding of the RV interval, indicating a constant time relationship between heart beat and the following ventilation. The number of bands indicates the entrainment ratio or number of heart beats within each ventilatory period.

Cardioventilatory synchronization was observed in two of eight subjects after administration of midazolam; one subject synchronized with a heart rate/ventilatory frequency ratio of 4:1 (fig. 1) and another at a ratio of 3:1. In both, synchronization persisted throughout the sedation period. Synchronization was not observed after placebo.

In the six other midazolam-treated subjects and in two placebo controls (one of whom had slept during the recording period), less distinct bands were observed in the RV plots. This is seen also in the subject in figure 1 in the 10 min before administration of midazolam. Closer examination of these bands showed them to be composed of variable numbers of heart beats during each ventilatory period (generally 3, 4 or 5). Despite this variability, RV intervals were within discrete bands. As we consider that these indicate a form of coupling between ventilation and heart beats, we refer to this phenomena as non-synchronous coupling (NSC).

In all midazolam-treated subjects, flumazenil ended the period of synchronization or reduced the clarity of the NSC bands.

During the period of synchronization shown in

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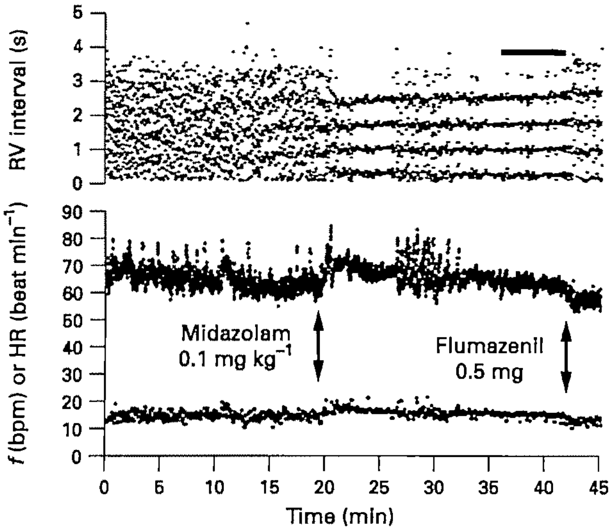

*Figure 1* RV interval, ventilatory frequency (*f*) and heart rate (HR) in a subject showing non-synchronous coupling (12–20 min) and 4:1 cardioventilatory synchronization after administration of midazolam. Occasional periods of 5:1 coupling are shown under the horizontal line.

figure 1, the ratio of heart beat to ventilation alternated between two whole number ratios (shown as a fifth sparse band between 35 and 40 min). During this episode, ventilation was constantly synchronized to every fourth heart beat but occasionally the following ventilation would be delayed while it "waited" for a fifth.

## Comment

Entrainment phenomena occur frequently in physical, mathematical and biological systems where two oscillators are coupled.[3] Many such entrainment phenomena have been described in physiology; breathing rate and heart rate may become entrained with step rate during running, cycling or rowing. In sleeping adults, the onset of inspiration most frequently occurs during the diastolic phase of the cardiac cycle[4] and the equivalent of our non-synchronous coupling has been described in sleeping infants.[5]

Some cardioventilatory interaction is necessary as conditions which increase heart rate tend also to demand increased ventilatory frequency. The benefits of NSC and synchronization are less clear. Several authors have argued that synchronization of locomotor and respiratory rhythms may cause a beneficial improvement in energy utilization, and in relation to our own observations, optimal pulmonary blood flow, gas exchange or cardiac work might best occur with a heart beat occurring during a particular phase of respiration. We believe that cardioventilatory coupling may be important for optimal performance of the thoracic pump which may require heart beat to fall within the range of the inspiratory period. If coupling is of benefit to the thoracic pump then plainly this effect is minimal in the awake and alert state. NSC and synchronization were observed only in subjects who were sedated or who had lain quietly for several minutes. This may suggest the role of coupling is evolutionally vestigial, or its role is important only during sleep.

The nature of the interaction between cardiac and respiratory rhythm generators is not understood with certainty. It is known that cardioventilatory entrainment ceases in animals when bilateral vagotomy is performed.[2] Thus efferent or afferent input from pulmonary stretch receptors or baroreceptors may play a part in the feedback interaction. In our study, NSC and synchronization were observed despite the mild vagolytic effect of midazolam (an increase in heart rate occurred in all midazolam-treated subjects and in none of the controls) (fig 1). Kenner, Pessenhofer and Schwaberger[2] found in rabbits "rapid and transient variations in the ventilatory rate appear to be mainly responsible for rapid entrainment". Similarly in humans we observed that entrainment of ventilation by heart rate clearly occurred where the respiratory period alternated between whole number ratios equal to the the heart period while heart rate remained relatively constant.

Goodman[6] noted that some anaesthetized patients exhibit a "bimodality of ventilatory frequency", that is ventilatory frequency settled at two possible values between which it variably alternated. Although the author suggested that this indicated the existence of a multi-frequency oscillator within the respiratory centre, the effect can be explained easily by cardioventilatory coupling, with ventilatory frequency varying between two entrainment ratios.

Current concepts of respiratory control focus on an independent respiratory oscillator modulated by chemo- and mechanoreceptor inputs. It is clear, however, that during sleep and sedation, the timing of ventilation is coupled or even synchronized for long periods to cardiovascular events. The clinical relevance of this coupling is unknown, although its recognition may have implications for the interpretation of studies involving analysis of heart rate variability, breathing periodicities and models of their genesis.

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CASE REPORTS

# Anaesthetic management of a patient with an automatic implantable cardioverter defibrillator *in situ*

P. C. A. KAM

## Summary

The automatic implantable cardioverter defibrillator (AICD) is becoming used more frequently in patients with refractory malignant ventricular arrhythmias. The anaesthetic implications of patients with an AICD *in situ* presenting for surgery are discussed. (*Br. J. Anaesth.* 1997; **78**: 102–106)

**Key words**
Equipment, defibrillators. Complications, tachycardia.

Malignant recurrent ventricular arrhythmias cause sudden cardiac death in an estimated 40 000 people annually in the United States.[1] Survivors of cardiac arrest secondary to ventricular tachycardias have a 30% risk of a recurrent arrest within 1 yr and a 45% risk at 2 yr.[2 3] The mortality rate is approximately 60% within 2 yr in spite of antiarrhythmic prophylaxis considered adequate at that time.[2 3] A major advance in the management of recurrent malignant ventricular tachycardia has been the development of the automatic implantable cardioverter defibrillator device (AICD) by Mirowski, Mower and Staewen.[4] Since the first device was implanted in 1980, technological advances have led to a marked increase in the insertion of AICD, especially with the availability of systems that do not require thoracotomy for implantation and further miniaturization of the generator.[5] Anaesthetists are therefore likely to encounter patients with an AICD *in situ* presenting for surgery unrelated to the defibrillator.

This article describes the anaesthetic management of a patient with a third-generation AICD *in situ* presenting for total hip replacement and discusses the management issues relevant to anaesthetists.

## Case report

A 62-yr-old man, a Jehovah's Witness with an implanted AICD, presented for left total hip replacement. He had a long history of hypertension and ischaemic heart disease for which he underwent coronary artery bypass surgery 5 yr and resection of a posterobasal ventricular aneurysm 2 yr previously. As he developed recurrent ventricular tachycardia (VT) and fibrillation (VF) with episodes of atrial flutter after the aneurysectomy, a third-generation AICD (Medtronic 7219C) with two transvenous leads and a subcutaneous patch electrode at the cardiac apex was implanted. The AICD was programmed to provide anti-tachycardia pacing of VT at 130–190 beat min$^{-1}$, low energy cardioversion for VT greater than 190 beat min$^{-1}$ and defibrillation at 25–35 J for VF with anti-bradycardia pacing at 50 beat min$^{-1}$. His current medications were sotalol 80 mg twice daily, captopril 25 mg daily, lisinopril 5 mg and frusemide 20 mg daily. He also had a history of mild obstructive sleep apnoea which was confirmed by sleep studies.

On examination, the patient was slightly overweight (90 kg) with an arterial pressure of 150/80 mm Hg and a heart rate of 60 beat min$^{-1}$. His ejection fraction was 30% and preoperative investigations were within normal limits. The preoperative electrocardiogram showed sinus rhythm with Q waves in the inferior leads.

All medications except frusemide were continued and he was premedicated with morphine 10 mg, 1 h before surgery. Before induction of anaesthesia, invasive arterial pressure, central venous pressure via an antecubital catheter, and ECG monitoring together with pulse oximetry were established. Adhesive external defibrillator pads were applied laterally on the chest away from the subcutaneous patches. A left femoral nerve block with 1% lignocaine 25 ml was performed. The patient's lungs were preoxygenated and anaesthesia was induced with increments of thiopentone to a dose of 175 mg i.v. Neuromuscular block was produced with vecuronium 10 mg and tracheal intubation performed. The patient's lungs were ventilated with 0.5–1% isoflurane and nitrous oxide in oxygen, and normocapnia was maintained with the aid of a capnograph. Normothermia (36.1 °C) was maintained with the use of a warm air convective blanket (Bair Hugger, Augustine Medical, USA) and an i.v. fluid warmer.

A programmer from the cardiology department was in attendance and the anti-tachycardia, cardioversion and defibrillation functions of the AICD were deactivated and the anti-bradycardia pacing function left intact. During operation, there was a transient episode of atrial flutter with a slow ventricular rate resulting in mild hypotension (75/50 mm Hg) and this triggered the anti-bradycardia pacing

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function of the AICD. The patient responded to metaraminol 0.5 mg and arterial pressure was maintained at 120–150/60 mm Hg with a CVP of 9–19 mm Hg.

Diathermy using bipolar leads was used throughout the procedure. A Muller cemented hip prosthesis was inserted. Blood loss was estimated to be 400 ml and the patient received 1 litre of normal saline. At the end of the procedure, neuromuscular block was antagonized with neostigmine 2.5 mg and glycopyrronium 0.4 mg.

In the recovery ward, the AICD was reactivated to its preoperative parameters. Analgesia was provided with morphine i.m. On the first postoperative day, the AICD was tested to ensure it was functioning appropriately. The patient was monitored in a high dependency area of the orthopaedic ward. However, the patient developed VT on the third and 10th postoperative days which was terminated successfully by anti-tachycardia pacing.

## Discussion

The AICD is proving to be an effective and innovative device for the treatment of patients with drug-resistant malignant ventricular arrhythmias, reducing the 1 yr mortality rate from 66% to approximately 8.5%.[6] An understanding of these devices is essential for anaesthetists who are likely to encounter these patients with an AICD *in situ* presenting for surgery unrelated to the device.

AICD technology[5 7 8] has become increasingly sophisticated and complex (table 1). The original first-generation AICD had only defibrillation capability without any programmability. The second-generation devices had limited programmability of rate threshold parameters and shock energy. The third-generation devices provide anti-bradycardia pacing, anti-tachycardia pacing, low energy cardioversion and standard defibrillation capabilities. The fourth-generation devices use a single right ventricular coil electrode and the body of the generator as the other pole for the delivery of the shock and are referred to as active or hot can devices.[8] Fifth-generation devices which have DDD pacemaker functions and can identify and treat atrial arrhythmias are currently undergoing clinical trials.

The AICD[5] consists of a pulse generator and a lead electrode system for sensing, pacing and delivery of shocks for cardioversion or defibrillation. The pulse generator is made up of a battery source (lithium vanadium silver pentoxide cells), capacitors for high voltage generation, and a storage and microprocessor logic system which analyses incoming signals and makes decisions regarding appropriate therapy based on algorithms set by the cardiologist. Older pulse generators weigh 200 g with a volume of 80–100 ml but newer devices may weigh 100 g with a volume of 60–100 ml. Larger generators are implanted in the left anterior abdominal wall behind the rectus muscle. The newer smaller generators[7 9] can be implanted in the pectoral region either subcutaneously or subpectorally.

Before 1990, the AICD used lead systems comprising epicardial patches which therefore required a thoracotomy. Non-thoracotomy lead systems[9] have become available over the past few years and consist of a ventricular lead with a distal sensing pacing tip and a defibrillation coil placed in the right ventricle. A second defibrillation coil is placed in the superior vena cava (SVC) or right atrium (RA), either on the same lead or on a separate lead positioned in the SVC or anchored to the RA. A third lead system usually comprising an array of leads placed subcutaneously over the cardiac apex may be required to achieve satisfactory defibrillation thresholds. The most recent advance has been the development of the active can system which uses a single ventricular electrode.

The sensing components of the AICD[5 7] continuously monitor and analyse the patient's heart rate (using the R-R interval) and waveform morphology by measuring the variance from baseline. The absence of isoelectric segments is typical of VF or sinusoidal tachycardias. Different emphasis on either the rate detection channel or the waveform channel may be selected by the cardiologist. Emphasis on the rate detection channel improves the detection of non-sinusoidal tachycardia but may sense and inappropriately deliver a shock in sinus tachycardia, supraventricular tachycardia or atrial fibrillation with a rapid ventricular response. With the fourth-generation devices, it is possible to programme to sense the rate of change in heart rate, therefore minimizing delivery of shock while the heart is in sinus rhythm. Dual sensing models have a better

*Table 1* Characteristics of automatic implantable cardioverter defibrillators (AICD) AB=Anti-bradycardia; AT=anti-tachycardia; LEC=low energy cardioversion; DF=defibrillation; pulses: +=present; −=absent, ±=limited, prog.=programmable; morph=morphology

| | Detection | | Pacing | | Therapy | | |
|---|---|---|---|---|---|---|---|
| Manufacturer/Model | Morph. | Rate | AB | AT | DF | LEC | Prog. |
| First-generation | | | | | | | |
| Intec aid | − | + | − | − | + | − | − |
| Second-generation | | | | | | | |
| CPI Ventak 1600 | − | + | − | − | + | + | ± |
| Third-generation | | | | | | | |
| CPI Ventak PRX1700 | + | + | + | + | + | + | + |
| Medtronics PCD 7215 | − | + | + | + | + | + | + |
| Fourth-generation | | | | | | | |
| CPI PRX 3 | + | + | + | + | + | + | + |
| Medtronic 7220 | + | + | + | + | + | + | + |

specificity for non-malignant arrhythmias but may not detect non-sinusoidal ventricular tachycardia. A malignant ventricular tachycardia is usually present for 5–15 s before the preset rate and morphology criteria are met, at which point the AICD charges its capacitor and delivers a shock of 25 J. The entire process takes 35 s and if VT persists, subsequent shocks of 30 J are delivered. After four shocks, the AICD resets in 35 s and if VT persists, another series of four shocks are delivered. The characteristics of the shock waveform (monophasic/biphasic) and current pathway (single, bidirectional or sequential) used in the AICD vary depending on the model and lead system used. The latest advanced AICD are capable of different responses to one or more tachycardias classified by rate and a programmable sequence or graded (or "tiered") therapy to an arrhythmia by providing adaptive pacing sequences to low energy cardioversion to high energy defibrillation. With the fourth-generation devices, the use of the large surface area of the "can" or body of the device as a pole for delivery of the shock decreases defibrillation thresholds and conserves battery life. If the malignant VT is shown to be terminated by pacing in the electrophysiology laboratory, algorithms may used to attempt pace termination of malignant arrhythmia. However, current devices may not be able to distinguish some forms of supraventricular and ventricular tachycardias, although atrial fibrillation may be identifiable if the variability in the RR interval is programmed into the device.

In the preoperative evaluation of patients[10] with AICD presenting for non-cardiac surgery, the underlying cardiac disease (ischaemic or valvular heart disease, cardiomyopathy) and the status of their ventricular function should be taken into account. It is important that these patients are receiving optimal medical therapy and a knowledge of preoperative antiarrhythmic medications for each individual patient would be useful if intraoperative VT or VF occurs. Preoperative investigations should be directed towards detecting any electrolyte imbalance or drug toxicity which may predispose to intraoperative complications or cause inappropriate discharge of the AICD. In the patient described, frusemide was omitted to reduce problems associated with hypovolaemia and haemodynamic instability. Patients with AICD frequently suffer from depression[11] as a result of the stresses associated with frequent discharges of the AICD and may be receiving antidepressant medication.

A knowledge of the model of the AICD is important as there is wide variation in the functional characteristics of different models.[5 7] Patients usually carry a medic alert bracelet[12] and identification data that would provide information on the model, lead systems, therapy options and contact details of the cardiologist. It would be prudent for the anaesthetist to consult the cardiologist involved. An over-penetrated radiograph of the pulse generator would identify the model of the AICD.[13] A chest x-ray would reveal the lead systems, position of the patches and pulse generator which are important for the intraoperative management of these patients.

AICD malfunction may be related to battery depletion, failure of sensing as a result of altered thresholds, and fracture or migration of lead systems. Cardiac symptoms may indicate the complications of AICD implantation such as infection, pericarditis, pericardial effusion, cardiac fibrosis or progression of the underlying cardiac disease.

Although there is little information available,[10] the anaesthetic management of patients with an AICD *in situ* is similar to that for patients with rate responsive permanent pacemakers.[14] In minor and short surgical procedures, monitoring should consist of ECG and pulse oximetry with a device that has a plethysmographic display. For major surgical procedures or patients with severe impairment of left ventricular function, intra-arterial pressure monitoring is mandatory as it would demonstrate the adequacy of perfusion in the event of intraoperative tachyarrhythmia. Central venous access and pressure monitoring is useful as it provides a route for vasoactive drugs and may aid in the optimization of fluid therapy. The use of a pulmonary artery catheter is dictated by the patient's cardiac function but its benefits must be weighed against the risks of inducing VT or VF and displacing the lead systems of the AICD during its insertion. An external cardioverter/defibrillator should be available in the operating theatre. Adhesive external defibrillator patches should be placed appropriately on the patient's chest and it is important to ensure that the appropriate connectors are available. These enable effective cardioversion/defibrillation without contamination or interference of the surgical field.

Although no specific anaesthetic techniques have been advocated, the main objectives are to avoid factors and drugs that induce VT or VF and to maintain haemodynamic stability. Adequate analgesia is essential to reduce sympathetic overactivity during and after operation.

In general, all AICD should be deactivated[8 12] during surgery as they can inappropriately discharge because of extraneous signals, such as myopotentials caused by shivering, or fasciculations induced by suxamethonium, diathermy, orthopaedic instrumentation, and by false sensing as a result of sinus tachycardia or rapid atrial fibrillation. However, with the third- and fourth-generation AICD, selective deactivation of the anti-tachycardia, low energy cardioversion and defibrillation functions can be achieved with the anti-bradycardia pacing function remaining activated. This is useful if the patient develops severe bradycardia during operation, as seen in this patient. Deactivation of the AICD is accomplished best using its programming device.[12] Deactivation of the first- and second-generation devices can also be achieved by placing a "ring" or "donut" magnet over the pulse generator for 30 s which is indicated by a continuous tone. Removal of the magnet maintains the pulse generator in its inactive mode. Reactivation of the AICD may be achieved by placing the ring magnet over the inactive pulse generator for 30 s, and pulse tones synchronous with the QRS complexes indicate that the generator is reactivated. However, the tones emitted from these devices are extremely difficult to hear. With the proliferation of new devices, the effects of a magnet are not consistent for all models of AICD.[13] The third- and fourth-generation devices are inhibited and continue to sense but not deliver therapy in the presence of a magnet.

Electromagnetic interference can lead to malfunction of the AICD.[10,13] High frequency electromagnetic interference can inhibit the AICD while lower frequency electromagnetic interference may cause the AICD to incorrectly sense and thus inappropriately deliver a shock. During surgery, if diathermy is used, the AICD should be deactivated to avoid inappropriate discharge and reactivated when diathermy is not required. In the patient described, diathermy was required to minimize intraoperative blood loss as he was a Jehovah's Witness. With the third-generation or multi-function AICD, VT and VF sensing and treatment functions should be programmed off, leaving the anti-bradycardia (VVI) pacing function intact. Diathermy can also cause burns at the myocardial–electrode interface leading to raised pacing thresholds, reprogramming of the AICD and damage to the circuit of the pulse generator. When diathermy is used, the following precautions should be undertaken.[15] Bipolar diathermy with the lowest current output should be used to prevent damage to the pulse generator. The ground or indifferent electrode of the diathermy should be placed as far away as possible from the generator. Diathermy must not be applied close to the generator as it may damage its circuitry and cause burns to the surrounding tissues.

Magnetic resonance imaging is contraindicated in patients with AICD[13] as strong magnetic fields produced can exert mechanical forces causing physical pain and damage to the generator, or cause inappropriate delivery of a shock. Radiotherapy (linear accelerator, betatron, radioactive cobalt) may damage the complementary metal oxide semiconductor circuits of the AICD, especially with cumulative doses.[13,16] Therefore, shielding of the generator should be undertaken and the device evaluated after its exposure to radiation. Theoretically, extracorporeal shock wave lithotripsy can produce mechanical and electromagnetic forces which can damage the piezoelectric crystal timing device of the AICD or cause inappropriate delivery of a discharge. However, bench analysis[17] and a case report[18] suggest that contralateral lithotripsy can be performed safely in patients with an AICD *in situ*. The safety of lithotripsy applied ipsilateral to the AICD is unkown. As electroconvulsive therapy (ECT) frequently induces transient arrhythmias, the AICD should be deactivated just before treatment and reactivated immediately after ECT.[13] Grounding of the patient should be avoided as the delivered current may be rerouted to the heart via the defibrillator electrodes resulting in VF.

The presence of an AICD should not discourage standard cardiopulmonary resuscitation.[12,13] External defibrillation does not damage the AICD and should be administered promptly on the assumption that the implanted device is not operative. With the first- or second-generation AICD, the presence of the epicardial patches may increase the energy required for external defibrillation as a result of the shielding effect of the insulating portions of the patches or the shunting of energy away from the myocardium through the conducting portions of the patches.[13] An anterior–posterior placement of external defibrillation pads has been shown to be efficacious in such patients.[19] In patients with subcutaneous electrodes requiring external defibrillation, significant interaction may occur if the chest paddles are applied over the subcutaneous electrode. After external defibrillation, the pulse generator should be examined for correct function and to ensure that the programmed parameters have not been reset. However, internal defibrillation can damage the AICD. Personnel administering cardiopulmonary resuscitation may experience a mild electric shock on the patient's body surface if an AICD discharges but this should not pose a risk to the personnel during resuscitation. Further, as rapid supraventricular tachycardias (SVT) with adequate perfusion are common during resuscitation, internal defibrillator discharges may be triggered by the SVT and result in VT or VF. Thus in a controlled environment it may be desirable to deactivate the AICD during cardiopulmonary resuscitation.

In the postoperative period, hypoxaemia, hypercapnia and inadequate analgesia causing increased sympathetic activity may predispose to VT and VF. Continuous monitoring is essential until vital signs are stable. Spontaneous skeletal muscle contractions caused by shivering can generate myopotentials which may inappropriately trigger the AICD. Low frequency electromagnetic interference may arise from transcutaneous electrical nerve stimulation (TENS) leading to inappropriate delivery of shocks and therefore are contraindicated.[15] It is imperative that the devices are tested before patients are discharged from hospital.

As automatic implantable cardioverter defibrillator therapy has become more popular and sophisticated, these devices present the anaesthetist with several diagnostic and management issues and hence an understanding of the functions of these devices is essential for the optimal care of the patient.

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# Ether in an isoflurane vaporizer and the use of vapour analysers in safe anaesthesia

A. N. STRACHAN AND M. N. RICHMOND

## Summary

A Penlon Sigma isoflurane vaporizer was found to contain some diethyl ether. This had escaped from a ruptured temperature compensation device within the vaporizer. The Datex AS/3 vapour analyser detected the foreign agent and displayed a warning. Different types of vaporizer compensation devices are highlighted and the use of vapour analysers is discussed. We conclude that these analysers are invaluable for indicating that the patient is receiving the correct concentration of an inhalation agent but are of little use in the detection of all but a few possible contaminants. (*Br. J. Anaesth.* 1997; **78**: 107–108)

**Key words**
Equipment, vaporizers. Anaesthetics volatile, diethyl ether. Anaesthetics volatile, isoflurane.

## Case report

A pungent smell of ether was noted from the common gas outlet at a routine anaesthetic machine check with oxygen flowing at 6 litre min$^{-1}$ and the vaporizer turned off. The Datex AS/3 agent analyser registered "alcohol detected". The machine was removed from service and the foreign agent was isolated to the Penlon PPV Sigma isoflurane vaporizer. Subsequent analysis of the contents of the vaporizer indicated the presence of diethyl ether. No other vaporizers in the department were found to have a similar problem.

The vaporizer was taken to be examined by the Medical Devices Agency. With the casing removed, a soldering defect was found in the bellows of the temperature compensation device which contains diethyl ether. Diethyl ether could escape into the bypass orifice and then into the back bar of the anaesthetic machine, even with the vaporizer turned off (fig. 1).

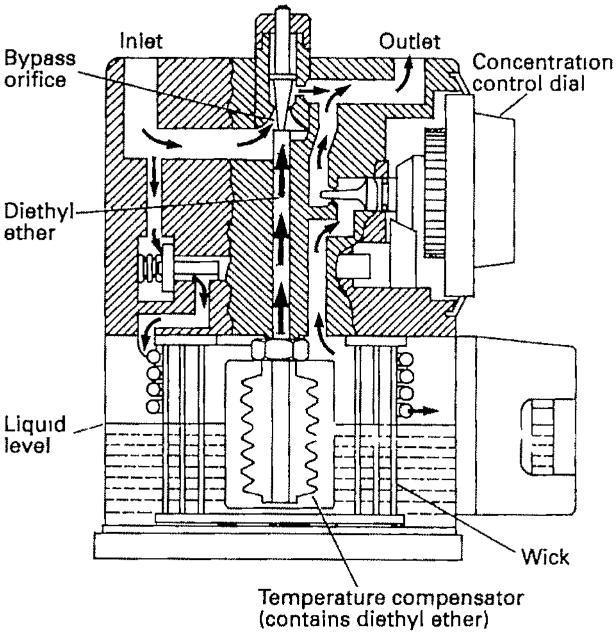
Inlet
Outlet
Bypass orifice
Concentration control dial
Diethyl ether
Liquid level
Wick
Temperature compensator (contains diethyl ether)

*Figure 1* Schematic diagram showing escape of diethyl ether from the temperature compensation device into the bypass orifice.

## Discussion

This case highlights several issues concerning vaporizers and vapour analyser design, particularly with regard to safe anaesthetic practice. Most anaesthetic vaporizers automatically compensate for temperature. Thermal compensation was first described as part of the Epstein–Macintosh–Oxford inhaler.[1] The diethyl ether filled bellows expands and contracts in one plane producing a linear change in gas flow resistance, allowing relatively simple calibration. Penlon continue to use this device in most of their vaporizers. In contrast, other manufacturers use bimetallic devices, with metals with different thermal coefficients of expansion (usually invar and brass) in varying designs to produce thermal compensation. They produce a non-linear change in gas flow resistance and are only accurate between 15 °C and 35 °C.

Vapour analysers in Britain are based usually on infrared absorption spectrophotometry. Light in the infrared spectrum does not cause damage to vapour molecules (ultraviolet light may ionize molecules and visible light may induce chemical reactions). Asymmetric polyatomic molecules absorb infrared light at characteristic wavelengths. Thus carbon

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dioxide has a strong absorption band at 4.26 μm and nitrous oxide has a dominant band at 4.55 μm and a weaker one at 3.9 μm. The volatile anaesthetic agents have a common band at 3.3 μm which corresponds to the stretching of the C—H bond, and a series of overlapping bands in the 7–14 μm range. The change in probe infrared light intensity caused by absorption can be used to determine the concentration of absorbing molecules. The vapour analysers thus use wavelengths in the range 3.3–3.5 μm and others up to 10 μm. They determine concentrations of the commonly used volatile anaesthetic agents and some are able to distinguish automatically between all five.

Infrared vapour analysers cannot detect chemicals outside their working wavelength, and can only detect a few chemicals within it. Unfortunately, some of these agents can interfere with this analysis. These include methane and acetone produced from the patient,[2 3] cyclopropane used for induction,[4] ethanol on the patient's breath and cleaning agents such as isopropyl alcohol used for breathing systems. The Datex AS/3 can detect the presence of methanol, ethanol, diethyl ether, acetone, isopropanol and acetaldehyde. In the presence of one of these contaminants the identification bench cannot ascertain a true concentration of anaesthetic vapour and thus displays an "alcohol detected" warning. Newer AS/3 monitors have an upgraded bench which automatically compensates in its calculations and produces a true vapour concentration. Thus this machine does not warn the anaesthetist even when such a foreign agent is detected.

The Association of Anaesthetists' guidelines state that the "monitoring of vapour concentration is desirable, particularly when low gas flows are used".[5] In surveys of anaesthetic mishaps, many include volatile anaesthetic agents. Five of 16 equipment faults in one survey resulted from a different agent, which had been used previously, being left in an operating mode.[6] Twenty of 507 equipment faults were caused by vapour overdoses and 22 by vaporizers being left in an operating mode unintentionally.[7] In the Australia incident monitoring study, three of 10 cases of awareness were caused by inappropriately low concentrations of inhalation agent.[8] Monitoring minimum alveolar concentration of inhaled agents may be the best currently available method of ensuring anaesthetic depth[9] and invaluable for medicolegal evidence.[10] Vaporizer settings may be inaccurate because of poor calibration,[6] overfilling[11] or emptiness.

In summary, this case has described a fault in a common design of vaporizer and highlights the use of the vapour analyser as a safety device as an indicator of appropriate concentrations of inhalation anaesthetic agent. Its use in detecting contaminants is severely limited but it would seem prudent that if a foreign agent is detected, even if the analyser can compensate, the anaesthetist should be warned.

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# CORRESPONDENCE

## Cardiac arrest after Caesarean section under subarachnoid block

Sir,—We wish to comment on the case report by Scull and Carli on cardiac arrest after Caesarean section during subarachnoid block.[1]

There seems to be little in common between the patient described by Scull and Carli and those in their references. In their discussion, Scull and Carli quoted case reports of excessive bradycardia progressing to asystole and differentiated between those patients with good and poor outcomes.[2–5] None of these patients was pregnant and all received sedative medication. Patients with a poor outcome appeared to be more profoundly sedated than those who did well. All those with a good outcome seemed able to converse with the anaesthetist until the time of the adverse event In only one of the patients under discussion was adrenaline used early in the course of resuscitation.[4] In Caplan and colleagues' group of 14 patients, adrenaline was not given until a mean time of 7.5 min after the diagnosis of inadequate circulation.[5]

Perhaps the important lesson to be drawn from this case report is that in any patient with inadequate circulation a resuscitation procedure should be used promptly. Use of either ventricular fibrillation or asystole procedures of the Adult Advanced Cardiac Life Support section of the European Resuscitation Council Guidelines would have resulted in more prompt administration of adrenaline with its beneficial $\alpha$ and $\beta$ agonist effects.[6]

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Sir,—The purpose of this case report was to highlight the potential for catastrophic cardiovascular collapse in patients with a high subarachnoid block. On reviewing the literature it became apparent that two groups of patients existed, those who immediately responded to minimal resuscitative measures[1–3] and those that, despite prolonged efforts, faired badly.[4 5] The idea that deeper sedation in the pre-arrest period seems to be linked to poor outcome was entertained briefly by Caplan and colleagues in their first reported series,[4] but was dismissed after analysis of the second series of cases.[5] The case we reported obviously does not fit into either category, indeed it is remarkable because of the duration of resuscitation and the resultant positive outcome.[6] We agree with Trotter and Patey that in the event of cardiovascular collapse, resuscitation procedures, that is early use of adrenaline, should be used.

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*Reading*

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Sir,—I read with interest the clinical report of Scull and Carli[1] describing cardiac arrest in a woman after Caesarean birth under subarachnoid anaesthetic. I wish to make two points. First, the dose of spinal bupivacaine was 15 mg which in my clinical experience is unnecessarily large. I have used 0.75% hyperbaric bupivacaine for Caesarean section in doses ranging from 1.0 ml (for short, oriental women whose obstetricians perform the surgery in less than 45 min) to 1.6 ml (in tall African American women where a larger dose is used to extend the duration of anaesthesia to allow for the inexperience of junior obstetric residents). The height of the sensory block varies among individuals but is always adequate for surgery (i.e. >T4). Interestingly, I have yet to witness maternal bradycardia with these doses, even when the sensory level has reached T2 or above. I wonder if the large dose of bupivacaine, used by these authors, place parturients at greater risk from a dense, high sensory block with an increased potential for bradycardia by mechanisms outlined in their discussion. I would wish to know at what point their patient's T2 sensory level was determined and what was the level 20 min after the block was instituted and at the end of surgery.

Second, the importance of hypomagnesaemia in this case may have been understated. Although serum magnesium concentrations decrease during pregnancy, perhaps as a result of a 25% increase in renal excretion,[2] they do not achieve the low concentration described in this woman (0.25 mmol litre$^{-1}$). Although no other risk factors for hypomagnesaemia were described in this report, they may have been present. For example, was there a history of hyperemesis gravidarum, use of diuretics during pregnancy or a history of alcohol abuse. Other possible causes exist[3] and needed to be excluded. On discovery of such a low serum concentration of magnesium, serum concentrations should be remeasured and, if still low, a 24-h urine collection for magnesium started. If serum magnesium concentration is <0.5 mmol litre$^{-1}$ and 24 h urine magnesium is <0.5 mmol, there is likely to be a total body magnesium deficiency which requires treatment and further investigation. The signs and symptoms of hypomagnesaemia can be subtle and include neuromuscular and psychiatric manifestations. If a pertinent history and physical examination are not carried out these problems can be overlooked. The cardiac manifestations of hypomagnesaemia are well described, especially in patients with heart disease and after cardiac surgery [4]

The initial ECG after collapse of the patient was ventricular fibrillation, well documented as a manifestation of hypomagnesaemia, especially torsade de pointes.[5] The 12-lead ECG findings in this patient were not described and although they are relatively non-specific in the presence of hypomagnesaemia, knowledge of the QT interval would be important. Treatment for ventricular fibrillation secondary to hypomagnesaemia is magnesium sulphate 8 mmol (2 g) i.v. over a 10-min period in 10 ml of 5% glucose in water, followed by 20 mmol in 500 ml over 3 h.

Scull and Carlis' report reminds us of the importance of having cardiopulmonary resuscitation (CPR) equipment available in obstetric suites and the need for regular CPR drills for medical, midwifery and nursing personnel. However, the aetiology of the cardiac arrest in the case they describe is not clear.

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Sir,—Thank you for the opportunity to reply to Dr Gambling

While we accept that an adequate block for Caesarean section may be obtained with a number of "recipes", it is our experience that hyperbaric bupivacaine 15 mg giving a block of up to T2 is optimum for the prevailing surgical conditions in our unit. The operative procedure may last up to 2 h with routine exteriorization of the uterus and a dense high block is preferable. Extreme bradycardia is rare, but reductions in maternal heart rate to 70–80 beat min$^{-1}$ are not unusual.

The sensory level of the block was determined with ice immediately before surgery, 15 min after dural puncture. The level was not checked during operation or at the end of the procedure. However, we do feel it is prudent to both check and document sensory levels at regular intervals during the operative phase and into the recovery period; this may provide useful information on recovery of sympathetic tone and hence the likelihood of triggering the detrimental circulatory reflexes discussed.

As reported in the case, the only abnormal finding on investigation of aetiology of the arrest was a low serum concentration of magnesium (0.25 mmol litre$^{-1}$). The patient had no risk factors for hypomagnesaemia such as those suggested by Dr Gambling She was investigated extensively for renal causes of hypomagnesaemia with no positive findings. After one bolus of magnesium in the post-arrest period, her serum magnesium concentration returned to and remained within normal limits. The 12-lead ECG revealed a sinus tachycardia with no QT abnormalities.

We agree with Dr Gambling that the aetiology of the cardiovascular collapse in this case is far from clear, although non-specific circulatory mechanisms as detailed in the case discussion[1] are the most likely cause.

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1. Scull TJ, Carli F. Cardiac arrest after Caesarean section under subarachnoid block. *British Journal of Anaesthesia* 1996; 77 274–276.

Sir,—We read the case report by Scull and Carli[1] and wish to make the following observations. Many factors may have contributed to the cardiac arrest in this patient but one factor may have been the choice of agents: 0.75% hyperbaric bupivacaine 2 ml and preservative-free morphine 0.25 mg to establish the subarachnoid block. These agents were chosen presumably to prolong the block (we sympathize with them in that the Caesarean section took 1 h 35 min) and provide postoperative analgesia. Bupivacaine 0.75% is not licensed for use in the USA or in this country after reports of maternal mortality.[2] It causes more profound hypotension than 0.5% bupivacaine[3] while the latter provides adequate anaesthesia for Caesarean section The risk of hypotension with the more concentrated solution cannot therefore be justified. The addition of intrathecal morphine further compounds the problem. Morphine is relatively lipophobic and tends to remain in the cerebrospinal fluid rather than bind to spinal receptors and rostral spread has been reported frequently[4] with potential respiratory depression The authors used naloxone but did not state if this reversed the apnoea. Intrathecal diamorphine which is more lipophilic[5] would have been the better choice with less risk of cephalad spread. Another method which would have prolonged the block without the use of opioids is a combined spinal and extradural technique.

We have no doubt that this block spread above the thoracic segments, as the authors stated that bilateral sensory block to temperature was T2 to S5 Anaesthesia is always at least two dermatomes above the sensory level to cold.[6] Further, the authors did not state when the block was tested but a subarachnoid block often takes up to 20 min to achieve its maximum dermatomal height

No mention of fluid loading was given other than after delivery when an infusion of Syntocinon in saline was started. Presumably some type of fluid loading had been given, otherwise significant hypotension secondary to sympathetic block would have occurred with a drastically reduced venous return initiating the reflexes mentioned in the original report.

We find it highly significant that the arrest occurred after patient transfer. In clinical practice, repositioning patients, especially transferring them from theatre to ward bed, can cause sudden and profound hypotension, presumably because of a surge of local anaesthetic or opioid towards the cardiorespiratory centres, although theoretically, the agents should have "fixed" by this time.

While appreciating that the patient was not monitored at the time of collapse, would asystole not be the more likely rhythm if the pathogenesis was progressive bradycardia and hypotension in a previously healthy 31-yr-old? Ventricular fibrillation is suggestive of electrolyte abnormality with hypomagnesaemia possibly the culprit.

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Sir,—Thank you for the opportunity to reply to Drs Burns and Clark. The use of 0.75% bupivacaine is not unusual in Canada, but we take the point that a more dense and prolonged sympathetic block may have contributed to the clinical scenario. However, hypotension was not a problem during operation. The patient received a preload of 1 litre of normal saline and the block was found to extend to T2, approximately 15 min after injection. Naloxone was given in the context of the arrest while IPPV was being administered, and therefore we cannot comment on its effect on respiratory depression.

We agree with Burns and Clark that the temporal relationship between the occurrence of cardiac arrest and transfer is highly significant. We feel, however, that the arrest was much more likely to have been caused by circulatory reflexes detailed in the report rather than "a surge of local anaesthetic or opioid toward the cardiorespiratory centres"

The presence of ventricular fibrillation does suggest an electrolyte abnormality; interestingly, Caplan and colleagues did not report on the presenting rhythm in their series of patients.

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## Haemoglobin changes during anaesthesia

Sir,—In the description of their study of the inter-relationships between hypotension caused by extradural block, i.v. fluid therapy and haemoglobin concentration,[1] Drobin and Hahn have not mentioned one possible explanation for the association they observed between changes in arterial pressure and haemoglobin measurement. This explanation relates to the phenomenon termed "plasma skimming".[2] Axial streaming of red blood cells may imply that blood entering small proximal vessels is relatively plasma rich with the result that whole-body packed cell volume is lower than that of blood sampled from a distal vessel. The vasodilatation that accompanies extradural block may disturb this process and result in a decrease in haemoglobin concentration measured in peripheral blood samples. Decreases of the same order noted by Drobin and Hahn have been observed when hypotension is induced by both halothane and extradural block,[3] and by sodium nitroprusside,[4] yet occur with minimal fluid therapy. I am afraid that such observations call into question the use of change in haemoglobin concentration as an indicator of the amount of i.v. fluid that is "retained" in the circulation during fluid therapy.

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Sir,—I wish to thank Dr Wildsmith for alerting me to this possibility. In my mind, however, plasma skimming occurs at the microvascular level[1] and the concentration of any substance in a large arm vein corresponds to the concentration on the arterial side, the difference being explained by cumulation in tissue. In the past, isotope studies indicated that the peripheral packed cell volume is only 91% of whole-body packed cell volume and this ratio was found to be stable over a wide range of clinical situations, including anaemia, moderate blood loss and spinal anaesthesia.[2–4] This packed cell volume factor was later attributed to the methods of measuring blood volume, and the current view is that the capillary bed is the only location in the cardiovascular system where a packed cell volume different from that in the large vessels can exist.[5]

Arterial samples may be studied to further elucidate if venous blood samples accurately represent average haemodilution in large vessels. Arterial blood summarizes what happens in the whole body, whereas venous samples also reflect events in the tissue drained by the vessel (such as plasma skimming). In a patient series that I collected 10 yr ago, most of which is as yet unpublished, blood haemoglobin concentration was measured in blood collected simultaneously from the radial artery and a cubital vein during the onset of spinal ($n=10$) or extradural anaesthesia ($n=22$) before short urological operations. Samples were collected before any fluid was given, when half the volume load of Ringer's acetate 10 ml kg$^{-1}$ had been given, and when all fluid had been infused and anaesthesia was established. The result is shown in table 1 and indicates that blood haemoglobin concentrations in arterial and venous blood of the arm are similar in the resting state, during ongoing volume loading and after spinal or extradural anaesthesia has just been induced. The small gradient that develops is likely to reflect cumulation of fluid in the tissue between the artery and the vein, just as would be expected during fluid loading.

*Table 1* Mean (SD) blood haemoglobin (Hb) concentration in arterial (A) and venous (V) blood during induction of spinal and extradural anaesthesia in 32 patients. *Analysed without extreme outliers (+10 to 11 g litre$^{-1}$), one for each point in time

| | | Hb concn (g litre$^{-1}$) | |
|---|---|---|---|
| Time | | A−V mean | A−V difference* |
| 0 min | Before fluid loading | 137.4 (13.8) | 0.0 (2.9) |
| 20 min | 50% of fluid load (total 10 ml kg$^{-1}$) | 131.7 (15.1) | −0.2 (3.1) |
| 40–45 min | 100% of fluid load Anaesthesia induced | 126.7 (14.6) | −0.3 (2.1) |

The haemodilution reported by Dr Wildsmith to be associated with the use of hypotensive agents probably represents a shift of interstitial fluid to the plasma, or else that most of the concurrently infused fluid remains in the blood. The second possibility is correct, at least in the case of extradural-induced hypotension, as no haemodilution occurs in the absence of i.v fluid administration.[6]

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## Unexpected difficulty in the lighted stylet-aided tracheal intubation via the laryngeal mask

Sir,—We reported that it was easy to pass a lighted stylet (Trachlight: Laerdal Medical Corporation, NY, USA) through the laryngeal mask into the trachea, and speculated that this stylet would facilitate blind tracheal intubation via the laryngeal mask.[1] We therefore planned a formal study in 40 patients to assess the efficacy of this technique.

After obtaining approval from the local research Ethics Committee and informed consent, we allocated patients randomly to one of two groups. In one group, tracheal intubation via the laryngeal mask was attempted with the use of the lighted stylet, whereas in the other group, it was attempted without the use of the stylet. The laryngeal mask was inserted and its position assessed using a fibreoptic bronchoscope A 6.0-mm Mallinckrodt reinforced tracheal tube, which is the largest size that can pass through the laryngeal mask and the longest (35 cm including the connector), was inserted with or without the lighted stylet through the laryngeal mask. Manipulation of the patient's head and neck or rotation of the tracheal tube was allowed only when there was difficulty in insertion of the tracheal tube Two attempts were allowed

We abandoned the study after 12 patients because, contrary to our speculation, it was almost always difficult to intubate the trachea via the laryngeal mask even when the lighted stylet was used. In patients in whom the lighted stylet was used, it was easy to intubate via the laryngeal mask in only one of six patients. In another patient, tracheal intubation succeeded at the second attempt after flexing the patient's neck. In the remaining four patients, it was impossible to intubate the trachea Without the use of the lighted stylet, tracheal intubation through the laryngeal mask succeeded in one of six patients at the first attempt and in another patient at the second attempt.

The success rate of blind tracheal intubation via the laryngeal mask may be very low, in particular when the position of the patient's head and neck is not manipulated [2,3] The Trachlight consists of a light wand and an inner malleable metal stylet When a curve is made to the stylet and the inner stylet is withdrawn for about 5–6 cm, the tip of the wand loses its rigidity and curves further anteriorly.[1] In the previous report,[1] this curve of the lighted wand allowed easy insertion of the lighted wand through the laryngeal mask into the trachea. In addition, if the lighted wand was impacted at the laryngeal inlet during insertion, it was possible to adjust the curve of the wand by withdrawing or re-inserting the inner metal stylet.

When the lighted wand was inserted as far as possible into the tracheal tube, the tip of the wand was positioned just short of the tip of the tube. When the metal stylet was withdrawn in this situation, the distal part of the wand and the tube curved only mildly, because of the rigidity and weight of the tube. In addition, when the wand and the tube were passed through the laryngeal mask, there was almost no movement of the distal part of the tracheal tube by withdrawal of the metal stylet because movements of the proximal part of the tube were restricted by the tube of the laryngeal mask. It is likely that this less effective control of the curve of the lighted wand led to a low success rate. Therefore, although it is possible that the success rate might be high if the Trachlight was longer than the current specification, the current Trachlight does not appear to be useful for tracheal intubation via the laryngeal mask.

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# BOOK REVIEWS

*Postoperative Management of the Cardiac Surgical Patient.* J. P. Williams (editor). Published by Churchill Livingstone, New York. Pp. 435; indexed; illustrated. Price £60.00.

Twelve chapters describing aspects of clinical management of patients after cardiac surgery are preceded by four chapters on the pathophysiology of adult heart disease and one outlining the pathophysiology of cardiopulmonary bypass. Each chapter is written by different authors from the USA or Europe, but the editor has managed to sustain an even style throughout

As the initial section title suggests, the mechanisms of preoperative disease are emphasized to give an understanding of the treatment principles to adopt. Regurgitant and stenotic valvular heart disease, cardiomyopathies and transplantation immunology are described in separate chapters, but it seems odd that the pathophysiology of ischaemic heart disease, which provides the most frequent indication for cardiac surgery, should not receive equal attention Cardiopulmonary bypass is considered separately. The technique is described and followed by an account of its effects on body systems.

The latter four-fifths of the book deal with clinical management. Chapters are devoted to individual body systems, nutrition, infection, pain management, cardiovascular pharmacology and mechanical circulatory support. By far the largest chapter is devoted to transoesophageal echocardiography and cardiac critical care. Forty-four pages include 10 figures, eight plates and 315 references up to 1995, and express the opinions of a committed enthusiast.

The text reads well, is given clarity by distinct sub-headings and is complemented by line diagrams and tables. The clinical management chapters include details such as drug doses and ventilator settings. The prescriptive approach is concise and straightforward and can easily be adapted if required. Where there is controversy or lack of evidence, this is declared. The book is written by anaesthetists and would be an excellent handbook for others about to be confronted by the care of patients after cardiac surgery.

*D J. R. Duthie*

*Key Questions in Anaesthesia,* 2nd Edn. T. M. Craft and P. M. Upton. Published by Bios Scientific Publishers, Oxford. Pp. 126. Price £12 95.

This book contains 360 multiple-choice questions arranged as four practice papers of 90 questions each. The book is marketed as a practice examination aid for trainee anaesthetists preparing for postgraduate examinations in anaesthesia. The format of the questions follows that of the multiple-choice papers of the diploma examinations for the Fellowship of the Royal College of Anaesthetists. The questions themselves are based on the parent publication, *Key Topics in Anaesthesia,* by the same authors and publishing house. This in itself immediately causes problems as the questions in *Key Questions in Anaesthesia* test the reader's knowledge of *Key Topics in Anaesthesia* rather than the subject area as a whole.

One could imagine therefore that it is quite possible to have a good recall of the information in *Key Topics in Anaesthesia,* therefore score well in the *Key Questions* practice papers, but do considerably less well when questions are not orientated towards the one particular source of information. This problem is clearly compounded when information in the parent book is wrong or, more likely in such a short text, does not give a balanced view of the literature on any particular topic. The candidate for the final FRCA examination might also come unstuck in using *Key Questions in Anaesthesia* as the only source of practice MCQ questions because of recent changes in the examination itself. In the new format of the final FRCA examination MCQ paper there is more emphasis on the applied basic sciences and intensive therapy: this is not reflected in the balance of questions in each of the practice papers in *Key Questions in Anaesthesia.*

Nevertheless, such books as *Key Questions in Anaesthesia* are useful for the examination candidate and this particular book is perhaps as good as any that this reviewer has considered. The candidate is well advised to note that all such publications undergo considerably less rigorous vetting of questions and answers than questions used in actual examinations and therefore contain a higher proportion of questions that might be considered ambiguous However, it is perhaps one useful function of these books that such perceived ambiguity may stimulate the candidate to return to the literature to improve his own understanding of the particular area. So while I would recommend examination candidates to purchase this book I would not go so far as the authors, who state that there is no substitute for practice in achieving high marks for MCQ. Rather, I would advise that there is no substitute for knowledge and how that knowledge should be applied to clinical practice.

*P. M. Hopkins*

*Pain Treatment Centres at a Cross-roads: a Practical and Conceptual Reappraisal.* M. J. M. Cohen and J. M. Campbell (editors). Published by IASP, Seattle. Pp. 338; indexed. Price $69.00.

This book represents the distilled procedures of a meeting held in Baltimore, USA, in March 1995. It reflects the view that, after a quarter of a century, multi-disciplinary pain centres are at a cross-roads and at a time for reflection and assessment of current treatment approaches in chronic pain.

It includes contributions from many of the early pioneers in the pain movement together with some young thinkers in the field and, interestingly, from insurance industry representatives

It acknowledges that chronic pain has developed rather quickly with some treatment approaches being accepted as the gold standard, without critical review. The book's contributors agree that this "young" discipline is at a cross-roads in maturation and deserves careful examination of its concepts and treatments. Several issues are propelled by the book, including the concept of assessment of economic pressures forcing all health care providers to scrutinize the rationales and outcomes of their work, and the sense of a less than full consensus regarding the focus and treatment of pain management. Several questions are raised, including the evaluation and treatment offered in multi-disciplinary pain clinics, the availability of data to validate varying approaches, the question of cancer treatment within the multi-disciplinary pain centre and the problem of funding of health care in pain work, especially in the USA.

The book consists of focused presentations on varying lessons from the past quarter century in the multi-disciplinary pain clinic. It is divided into sections covering the spectrum of pain centre outcome of treatments, social and economic impact of pain and pain as a distinct speciality. It is wholly American, but undoubtedly relevant to pain practices in the UK. It acknowledges the "hidden back road" status of the pain clinic in the USA and the need for them to emerge as a "grand boulevard" in the health care system

*M. Bone*

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*"I would have everie man write what he knowes and no more."*—MONTAIGNE

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## EDITORIAL I

# Extradural analgesia: does it affect progress and outcome in labour?

Extradural analgesia has been used to relieve labour pain in many obstetric units for more than two decades, yet controversy persists about its effect on progress and outcome in labour. There is general agreement that extradural analgesia increases the chances of a mother requiring an instrumental (forceps or Ventouse) delivery and prolongs the second stage of labour, although it is difficult to quantify this effect. Recently there has been debate on the influence of extradural analgesia on Caesarean section rates, with Thorp and colleagues suggesting its increasing use has played a significant role in the increasing rate of Caesarean section.[1] In the Cochrane Pregnancy and Childbirth Database (CPCD), Howell concluded that while extradural analgesia achieves better pain control than non-extradural analgesia, it does so at the expense of longer first and second stages, increased use of oxytocin, a two-fold increase in malrotation of the fetal head, a four-fold increase in instrumental deliveries and an unquantified increase in rate of Caesarean section for failure to progress.[2] If true, this would have a major impact on the information we should give parturients before siting an extradural catheter for analgesia in labour.

Millions of women have received the benefits of extradural analgesia in labour but few have participated in studies comparing extradural analgesia with other forms of pain relief.[3] Obstetric anaesthetists have been accused of "not living up to their responsibilities" by failing to undertake relevant randomized, controlled studies.[4] Several practical and ethical considerations make large studies difficult, if not impossible. Most women have firm views on the form of analgesia they prefer in labour. They might *change* their views during labour, but few are likely to consent to receive a pre-determined method of analgesia throughout labour. Would such a study be ethical given that extradurals give better pain relief than systemic opioids, which have depressant effects on the mother and fetus, and that women who have an extradural are less likely to receive a general anaesthetic with its associated problems if an emergency Caesarean section is required?

Two prospective, randomized, controlled studies comparing the impact of extradural with systemic opioid analgesia on the progress and outcome of labour have been completed; one in Denmark, the other in North America. Both studies were similar in size (112 and 93 patients) but their results differed. Philipsen and Jensen[5] found similar instrumental and Caesarean delivery rates in the two groups, although the Caesarean section rate was not significantly higher in the extradural group (17% and 11%, respectively). Extradural analgesia was discontinued at 8 cm cervical dilatation.[5] In contrast, Thorp and co-workers[1] demonstrated an 11-fold increase in Caesarean section rates in the extradural group (25% compared with 2.2%), the majority of which resulted from dystocia (16.7% *vs* 2.2%). Almost all women in the extradural group who required Caesarean delivery had received extradural analgesia early in labour (before 5 cm cervical dilatation). The authors concluded that women should be warned that they are more likely to require Caesarean delivery before receiving extradural analgesia and that extradural analgesia should be delayed until the cervix is more than 5 cm dilated.

The results of Thorp and co-workers' study have heavily influenced the conclusions drawn by Howell in the CPCD[2] and by the authors of another meta-analysis undertaken to investigate the impact of extradural analgesia on outcome of labour.[6] It is therefore appropriate to scrutinize the methodology of Thorp and colleagues. Criticisms have been numerous and many are fair. The authors of the paper were the clinicians responsible for deciding what constituted an arrest of first and second stage labour (dystocia) and investigators were not blinded to the analgesic method. There were no guidelines for management of labour or for oxytocin administration. Nevertheless, although this study has provoked much discussion and dissension, in the absence of other randomized, controlled studies it will continue be to cited as evidence that extradural analgesia in labour has a profound effect on labour.

Many non-randomized, uncontrolled studies have shown that extradural analgesia in labour is *associated* with longer labours and increased instrumental and Caesarean deliveries,[7 8] but whether this relationship is *causal* remains unclear; conversely it has been shown that increasing extradural rates do not necessarily result in increasing instrumental or Caesarean deliveries.[9] The downfall of many studies is their inevitable selection bias—women who request extradural pain relief in labour are more likely to be having longer, more painful or induced labours than those who do not and are also more likely to require operative delivery (instrumental or Caesarean).[10] What effect the extradural *per se* has on outcome is impossible to quantify.

What effect does obstetric management have on the outcome of labour? Giving oxytocin during labour and allowing a longer, second stage of labour promote normal vaginal delivery.[11] Adopting an active management of labour policy, with strict criteria for diagnosis of labour and oxytocin augmentation if required, can reduce instrumental and Caesarean deliveries. In one study of 1000 actively managed nulliparae, the Caesarean section rate was 5.6%, despite an extradural rate of 31%.[12] In a large observational study of 1250 primiparae, 67% of 568 women who received an extradural achieved a normal vaginal delivery when an active management of labour policy was used.[13] Women undergoing induced labours are more likely to require Caesarean or instrumental delivery, regardless of analgesic technique, and therefore induction rates affect operative delivery rates.[13 14] Induction, extradural, instrumental and Caesarean delivery rates vary greatly between hospitals and between individual clinicians; there are many factors other than extradural rates which contribute to the outcome of labour.[15]

Does modification of anaesthetic management influence obstetric outcome? Stopping extradural analgesia before the second stage promotes normal delivery, although at the expense of increased pain, which is unlikely to be popular.[16] In contrast with Thorp's data, Chestnut and colleagues have clearly demonstrated that early rather than late extradural placement does *not* increase operative deliveries.[14 17] In 1981, Thorburn and Moir, in a study of 517 women allocated randomly to receive either 0.25% or 0.5% extradural bupivacaine, showed that concentrated local anaesthetic solutions increased forceps delivery rates.[18] Many studies have aimed to minimize motor block by using low-dose bupivacaine–opioid mixtures which provide analgesia comparable with stronger bupivacaine but reduce total bupivacaine dose and its associated motor block. Two studies have shown that such combinations may reduce operative deliveries. Vertommen and colleagues' study of 695 women receiving extradural analgesia in labour showed that the addition of a lipophilic opioid (sufentanil) to 0.125% bupivacaine reduced bupivacaine requirements and the incidence of instrumental deliveries from 36 to 24%.[19] In a smaller UK study of 85 primiparous women, those who received low-dose bupivacaine and fentanyl were more likely to have a normal delivery than those receiving 0.25% bupivacaine.[20] It would appear that modification of anaesthetic practice may promote normal delivery but it would be fair to say that this remains controversial and many studies have failed to confirm these conclusions.

What remains unclear is *how* extradurals modify labour. In *second stage* labour there is evidence that extradural analgesia attenuates endogenous oxytocin production (Ferguson's reflex)[21] and reduces uterine contractility.[22] It is assumed that the motor block associated with extradural analgesia causes relaxation of the pelvic floor, predisposing to malrotation of the fetal head and reduces maternal effort during pushing. As regards *first stage* labour, extradurals do not appear to reduce uterine contractility, although cervical dilatation may be slower.[23]

Many factors can modify uterine contractility.[24] In a recent issue of the journal, Cheek and co-workers,[25] in a randomized, controlled study of 34 women in spontaneous labour, showed that administration of 1000 ml of normal saline fluid load before insertion of an extradural decreased uterine activity for 10–20 min. A smaller 500 ml load did not have a significant effect. Subsequent institution of an extradural block did not affect uterine activity. It was not apparent that the transient reduction in activity modified the overall progress of labour but it is important that obstetric anaesthetists avoid factors which may modify uterine activity. Thorp and colleagues fail to provide information on fluid preload before extradural insertion[1] but it is common practice in North America to fluid load with at least 1000 ml of fluid.

Does the effect of a fluid load on uterine activity affect European anaesthetists? While giving an i.v. fluid load before extradural *analgesia* is not routine practice in the UK, it is before regional *anaesthesia* for Caesarean section, when a profound, high sensory block is accompanied by widespread sympathetic block. This practice has been questioned recently by Jackson, Reid and Thorburn who showed that a 1-litre fluid load failed to reduce the incidence or severity of hypotension associated with subarachnoid block for Caesarean section.[26] It is therefore unnecessary, and possibly detrimental to uterine activity, to fluid load before extradural analgesia for labour.

In summary, while it is impossible to exonerate extradural analgesia in labour from modifying the course of labour, the suggestion that extradurals are important contributors to increasing Caesarean section rates should be repudiated. The knee jerk reaction of obstetricians to blame anaesthetists for obstetric interventions should be resisted. Any impact of extradurals on outcome of labour is overshadowed by that of obstetric practice. Nevertheless, it is important that obstetric anaesthetists continue the search for an extradural technique which minimizes side effects, introduce such techniques if they are shown to be beneficial and encourage obstetricians to adopt policies which promote normal deliveries. For the foreseeable future extradural services will be essential to modern obstetric practice; extradurals can provide pain relief superior to all other forms currently available, and although many women in the UK may not *plan* to use it, it is clear that many request it during labour and are disappointed if it is not available. Labour can be extremely painful for many women. They are entitled to receive extradural analgesia if they wish without being exposed to unsubstantiated scare stories about its side effects.

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EDITORIAL II

# Recent advances in prophylaxis against deep vein thrombosis

Deep vein thrombosis (DVT) is a condition which presents a diagnostic and therapeutic challenge to all clinicians directly involved in patient care. The spectrum of acute disease ranges from asymptomatic thrombosis (typically affecting distal, calf veins) discovered incidentally at autopsy or during screening procedures, through to the classic swollen, red, painful leg, to the potentially fatal complication of pulmonary embolism. In the long term DVT may lead to the troublesome post-thrombotic syndrome of persistent swelling, pain, pigmentation and ulceration, and this can affect up to 25% of patients with DVT.[1 2] It is difficult to determine a value representing the true incidence of this disease as it is well documented that many DVT are not detected clinically[3–6]; however, the fact that it is a significant problem is well recognized. A study in 1988 in the UK found that 0.9% of all admissions to hospital suffered fatal pulmonary embolism as a result of DVT,[4] and the incidence of DVT in surgical patients is 10–80%, depending on the type of surgery and individual patient risk factors.[7–10]

As always, prevention is better than cure, and apart from the obvious benefit to patients, prophylactic measures against DVT are cost effective through reduction in fatal complications and treatment requirements.[10 11] It has been estimated in the USA that widespread use of prophylactic measures in surgery would save $60 per operated patient.[12] Over the course of the past 5–10 yr there has been an increasing awareness of the importance of DVT prophylaxis, stimulated in particular in the UK by the reports of the THRIFT (Thromboembolic Risk Factors) Consensus Group and the National Confidential Enquiry into Perioperative Deaths 1992,[9 13] and a great deal of effort has been put into developing safe and effective methods of prophylaxis.

There are already several different, effective methods of DVT prophylaxis available, which are traditionally divided into two categories: physical and pharmacological methods. Graduated compression stockings are the most popular physical method, with intermittent compression devices being more cumbersome to use and less well tolerated. Low-dose heparin is the mainstay of pharmacological prophylaxis, with a wide variety of other drugs being used with varying degrees of success (warfarin, aspirin, dextran, dihydroergotamine). In the face of existing, effective measures, the recent advances in this field have been refinements of tried and tested methods, and they are described here.

## Physical methods

### INTERMITTENT COMPRESSION DEVICES

Intermittent pneumatic compression (IPC) of the lower limbs has been used over the past 30 yr, and while the original compression boots were uncomfortable and tolerated poorly[14] modern designs with sequential pressure application have been more widely accepted. IPC works both by eliminating venous stasis with generation of pulsatile blood flow (simulating the effect of the "muscle pump") and by stimulating fibrinolysis.[15 16] The most recent addition to the range of devices available is the arterial–venous impulse foot pump which is applied to the patient's foot and provides compression to the plantar venous complex. This device has been used mainly in orthopaedic patients undergoing knee and hip surgery where it has significantly reduced the incidence of DVT.[17–20] Its advantages include good patient tolerability compared with conventional IPC boots enabling it to be used after operation until the patient is mobile, and avoidance of the haemorrhagic complications associated with other methods of prophylaxis. So far it has been evaluated only in knee and hip surgery, and it may not be as effective as existing IPC devices.

## Pharmacological methods

### LOW MOLECULAR WEIGHT HEPARIN

Heparin exerts an antithrombotic effect by binding to, and accelerating the activity of, two cofactors; antithrombin III and heparin cofactor II. The rationale behind the use of low-dose heparin as prophylaxis is that only small amounts of the drug are required to inhibit the clotting cascade in its early stages, before coagulation is established, and conventional, unfractionated heparin has been used in this way since the 1960s.[21] A meta-analysis of more than 70 randomized, placebo-controlled studies in 1988 showed that the incidence of DVT was reduced by 66% and the incidence of pulmonary embolism reduced by 50%[10] with unfractionated heparin administered subcutaneously in low dose (5000 u. 8 or 12 hourly).

Recent interest in heparin prophylaxis has centred on low molecular weight heparins, so called because their range of molecular weight is 2000–8000 Da, compared with 5000–30 000 Da for unfractionated heparin.[7] Low molecular weight heparins have several differences from unfractionated heparin, apart from molecular weight, which help to explain their therapeutic advantages. Low molecular weight heparins have a much greater anti-Xa than anti-IIa activity, which theoretically makes them more effective at preventing thrombin formation than unfractionated heparin with an equal anti-Xa and anti-IIa ratio, and *in vivo* activity certainly shows good correlation with anti-Xa activity.[22 23] Low molecular weight heparins have a bioavailability approaching 100%, compared with 30% for unfractionated heparin, and a half-life after subcutaneous injection of 3–5 h, enabling a single dose to provide effective anti-thrombotic activity for 24 h.[22 24] The smaller charge density and chain length of low molecular weight heparins decrease their binding to several proteins (platelet factor 4, lipoproteins, fibronectin and protamine), endothelial cells, macrophages and platelets.

Low molecular weight heparins are at least as effective as unfractionated heparin at preventing DVT in both general and orthopaedic surgery, and the incidence of bleeding episodes is not significantly different between the two in most studies so far.[22 25–27] The one area where low molecular weight heparins show an undisputed advantage is that of convenience and patient acceptability; the once-daily dose is easier for nurses and patients, and there is significantly less bruising at injection sites.[25]

### ORGARAN

Orgaran is a low molecular weight heparinoid consisting of a mixture of heparan sulphate, dermatan sulphate and chondroitin sulphate, chemically distinct from heparin. Although not in widespread use it has been evaluated in several studies of patients at high risk of DVT, where it has been shown to be effective and comparable with low-dose heparin.[28]

## Guidelines

DVT prophylaxis is effective only if it is given to the correct patients for the correct period of time, and the development of hospital guidelines to ensure that this happens is probably as important as any therapeutic advance. A guidelines should enable classification of patients admitted to hospital as to their degree of risk, and the recent recommendation of the European Consensus Group can be summarized as follows:

- Low-risk patients:
  - <40 yr old without additional risk factors.
  - Minor surgery (<30 min).
- Moderate-risk patients
  - >40 yr old.
  - Oral contraceptive medication.
  - Major surgery (>30 min).
  - Immobilized medical patients with active disease.
- High-risk patients
  - Previous DVT/PE.
  - Major surgery for malignant disease.
  - Orthopaedic surgery to lower limbs.
  - Stroke, congestive cardiac failure and acute myocardial infarction.

(Adapted from the European Consensus Statement [29]).

Low-risk patients may not benefit from prophylactic measures, but all moderate- and high-risk patients should be offered prophylaxis as a matter of routine. The preferred type of prophylaxis varies from hospital to hospital, and even between hospital departments, the most important factor being that patients are assessed correctly for risk and the relevant local policy then implemented.

## Surgical specialties

Different specialties have particular considerations which influence the choice of prophylaxis.

### OBSTETRICS AND GYNAECOLOGY

Young women receiving the oral contraceptive pill (OCP) are in at least the moderate-risk group and should discontinue this 6 weeks before elective surgery, or should be given subcutaneous heparin and/or compression stockings if admitted as an emergency. Hormone replacement therapy (HRT) has not been shown to increase the risk of thromboembolic disease, but patients receiving HRT are aged more than 40 yr of age and should therefore qualify for prophylaxis. Some clinicians would advise patients to discontinue HRT 6 weeks before elective surgery as for the OCP.

### UROLOGY

Because of the endoscopic nature of most urological surgery, haemostasis is not as easily secured as during open surgery. Consequently, any drugs which predispose to bleeding are avoided as far as is possible, aspirin in particular being stopped 2 weeks before elective transurethral surgery. Heparin is avoided as a choice for prophylaxis, and mechanical methods are preferred.

### ENT

Major head and neck surgery is performed on a part of the body renowned for vascularity, and therefore mechanical prophylaxis is preferred rather than pharmacological methods with their increased risk of postoperative bleeding.

### NEUROSURGERY

These patients have a similar risk of DVT as general surgical patients,[24] but the consequences of an intracranial bleed are so severe that, as with ENT, mechanical methods are preferred.[14 30]

## Summary

The major development in DVT prophylaxis in recent years has been the introduction of low molecular weight heparins. Their main improvement compared with unfractionated heparin is in the convenience of a once daily dosage, but they have not yet convincingly been shown to be more effective or safer.[22 23] A-V impulse boots may have an impact on knee and hip surgery but still face problems with patient acceptability. Probably the best way to ensure that more DVT are prevented is by clinicians maintaining a high level of awareness of the risk, and developing, and adhering to, local guidelines.

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# EDITORIAL III

## Thermoregulation in critical illness

Mammals owe their success, in part, to the ability to maintain their central body or core temperature within narrow well defined limits. The survival value of such a facility (being able to carry out high rates of muscular, neuronal and cellular work independently of environmental temperature) is obvious.[1] Body temperature is "set" within the central nervous system. The areas associated with temperature control lie in the hypothalamus and preoptic region. There are two distinct groups of neurones concerned with temperature control, one promotes heat loss, the other heat production and conservation. The principal synaptic mediators are noradrenaline, associated with heat loss, and 5-hydroxytryptamine, associated with conservation of heat. Acetylcholine is associated with the mechanisms whereby heat is lost or conserved (sweating, shivering, etc).

Heat is produced in humans for "basal" requirements (maintenance of cell membrane potentials, the energy cost of the beating heart, of breathing, etc.), absorption and assimilation of food, and muscular activity. The traditional view has been that non-shivering thermogenesis in adult humans, as mediated by brown adipose tissue and seen in hibernating animals and in the human neonate, does not exist, although the subject has been highly controversial.[3–5] Humans defend their body temperature from a cold stimulus mainly by behavioural means—seeking shelter, lighting a fire and putting on more clothes. Physiological mechanisms include peripheral vasoconstriction and perhaps increasing food intake, but the only means of significantly raising heat output is by muscle contraction—exercise, shivering and an increase in muscle tone. Acclimatization to cold is thought to be limited to an increase in the efficiency of the peripheral vasoconstrictor mechanisms.[1] Acclimatization to heat, in contrast, is well documented and accompanied by increased sweat rates, an increase in blood volume and a decrease in the $Na^+$ and $Cl^-$ content of sweat and urine.[1] The range of body temperature within which the individual can survive is between approximately 25 °C (representing a heat debt of approximately 700 kcal) and 42 °C (representing a heat gain of approximately 360 kcal). The limits within which homeothermy can be maintained and the organism function effectively are from 35–36 to 41 °C.[1] Both trauma and infection alter the temperature at which the body "sets" its internal environment and in general, temparature is increased.[6] In addition to external pyrogens the mediators of this change in temperature control are the various cytokines such as interleukin-1[7] and tumour necrosis factor[8] and they act within the hypothalamus, promoting prostaglandin synthesis.

Over the past 20 yr we have become increasingly aware that during surgery patients' temperatures tend to decrease, that this is worse in the very young, in the very old and in surgery that is prolonged.[9] Postoperative recovery from intraoperative hypothermia is associated with severe metabolic disturbances in terms of counter-regulatory hormone secretion[10] and increases in energy expenditure (shivering) with its associated cardiovascular stress[11] and potential for hypoxaemia.[12] More long-term problems are disturbances in protein metabolism[13] and loss of lean tissue,[14] but on recovery of consciousness the individual is able to respond.[15] On awakening, muscle tone and metabolic rate increase and body temperature increases up to or exceeds preoperative values reasonably quickly.[15,16]

In the (adult) intensive care unit hypothermia is not generally a problem, despite patients being nursed virtually naked, under relatively insubstantial coverings, frequently bed-bathed, kept sedated to varying degrees, sometimes paralysed completely and at several degrees below that usually considered as thermoneutral. A recently published textbook on intensive care[17] mentions disturbances in temperature control only as a specific injury or secondary to a specific pathology, not as a particular problem of medical or nursing care.[17]

In acute and critical illness however, hyperthermia, or fever, can be a problem. Even simple trauma or surgery, as part of the acute phase response, results in an increase in body temperature.[6,18] With infection, pyrexia is usually quite marked. This may have positive[19] or negative[20] effects on the body's ability to respond to the invading organism, but it can be uncomfortable for the patient and alarming for his or her attendants. The intuitive response is to take steps to reduce a high fever, normally with antipyretic agents, or in more severe circumstances by "tepid sponging".[21,22] The usual concern about applying ice cold water to the pyrexial patient is the danger of inducing peripheral vasoconstriction, reducing peripheral heat loss and making the pyrexia worse.[1,23]

In this issue of the journal, Poblette and colleagues describe the results of manoeuvres designed to reduce pyrexia in sedated patients undergoing artificial ventilation.[24] Two centrally acting antipyretic agents were tried; they did nothing, but overall surface cooling with cloths soaked in iced water produced a rapid and effective decline in body temperature of 2 °C, a decrease in heart rate and a decrease in oxygen consumption of 12%. Perhaps surprisingly temperature remained reduced and there was no evidence of shivering. The antipyretics are thought to work by inhibiting prostaglandin synthesis in the brain.[25] Whatever the mechanisms, they did not work in this instance, but ice-cold water did. One might have expected such a severe peripheral stimulus to have elicited the responses to protect body temperature discussed above—peripheral vasoconstriction and an increase in muscle tone. In the one patient who was not sedated, body temperature increased with an increase in energy expenditure of 100%, but with no visible signs of shivering.

None of the patients was paralysed. Apart from the individual noted, all were sedated with morphine and midazolam, but we are given no indication of their level of consciousness. The reduction in energy expenditure of 6% $°C^{-1}$ is comparable with previous values published for this type of patient[26 27] and contrasts with that of 13% $°C^{-1}$ usually quoted for normal, conscious individuals.[28]

The decrease in central temperature in response to the treatment with iced water implies an inability to defend body temperature adequately in these particular circumstances. The most likely causes are the drugs used to maintain sedation (morphine and midazolam). It is not entirely possible to exclude the effects of the illness itself, but anaesthetic and analgesic drugs are known to inhibit thermoregulatory responses (the inhalation agents being the worst), both by central and peripheral mechanisms.[29–32] It appears that this allows us to manipulate body temperature in severely ill patients to a degree, and in a fashion, that in the unsedated individual would not be possible. In view of the rapidity with which postoperative patients regain normal temperature however one cannot help but wonder if the ability to defend or regain core temperature is related also to level of consciousness.

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CLINICAL INVESTIGATIONS

# Metabolic effects of i.v. propacetamol, metamizol or external cooling in critically ill febrile sedated patients

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## Summary

We have measured the metabolic response to sequential administration of propacetamol, metamizol and/or external cooling in 20 febrile patients under sedation and analgesia and during mechanical ventilation. There was no change in temperature (T°) after propacetamol therapy, whereas after metamizol only a small decrease was noted (from 38.9 (SEM 0.2) to 38.5 (0.3) °C; $P=0.02$). External cooling produced a significant decrease in T° (39.1 (0.2) to 37.1 (0.2) °C; $P<0.0001$) accompanied by a decrease in energy expenditure (EE) (2034 (73) to 1791 (88) kcal day$^{-1}$; $P<0.004$). Heart rate and minute ventilation decreased significantly in parallel. There were no other changes in haemodynamics or pulmonary gas exchanges. We conclude that propacetamol and metamizol did not produce a clinically significant decrease in T° in febrile ICU patients whereas external cooling decreased both T° and EE. The parallel decrease in body temperature and EE seemed to be related to opioid administration or sedation, or both. (*Br. J. Anaesth.* 1997; **78**: 123–127).

**Key words**
Temperature, monitoring. Temperature, metabolism Measurement techniques, calorimetry Intensive care.

Fever in critically ill patients is related frequently to either the systemic inflammatory response syndrome (SIRS) or infection. Usually fever is treated with antipyretic drugs, often paracetamol or metamizol. External cooling by different methods, such as sponging the body surface with ice-cooled water, is also used.[1] Even if reducing fever is still controversial from an immunological point of view, there is little doubt that patient comfort and metabolic demand can be improved by this procedure.[2] Indeed, a previous study in critically ill patients demonstrated diminished oxygen consumption related to decreased body temperature improving the oxygen demand–delivery ratio.[3] However, body cooling in healthy humans results in shivering which increases energy expenditure (EE).

The aim of this study was to measure EE as an integrated indicator of body metabolic activity after reduction in temperature. Our hypothesis was that external cooling may induce an increase in EE, in contrast with drugs which, by resetting the thermoregulatory set point, decrease EE. Therefore, we designed a prospective, unblinded, crossover study to evaluate the respective effects of centrally acting drugs (propacetamol or metamizol) or external physical cooling in febrile ICU patients.

## Patients and methods

The study was approved by the Ethics Committee of our institution. The requirement for informed consent was waived by the committee who judged that the therapies were applied independently by the attending physician and were accepted in clinical practice, and no invasive measurements were made. We studied 20 patients undergoing mechanical ventilation via a tracheal tube, with a rectal temperature greater than 38.5 °C and in whom the physician in charge wished to decrease fever. No patient had an inspired oxygen fraction greater than 0.6, a pneumothorax or a broncho-pleural fistula. Patients' lungs were ventilated with a Veolar-Hamilton (Hamilton Bonaduz, Switzerland) or Engström-Erica ventilator (Engström, Bromma, Sweden). Ventilatory settings, adjusted to obtain normal arterial blood-gas tensions, were maintained constant during the study. No patient received a caloric intake exceeding the measured EE at baseline. Analgesia and sedation were adjusted to obtain clinical comfort of the patient, as judged by nurses and physicians, by a continuous and constant infusion of morphine 2–6 mg h$^{-1}$ and midazolam 2–10 mg h$^{-1}$ to obtain a sedation level of 3–4, according to the score of Ramsay and colleagues.[4] Patients were kept supine during the study.

The following variables were monitored continuously: rectal temperature, heart rate and arterial pressure, ventilatory frequency, tidal volume; inspired and expired minute ventilation were recorded from the ventilators. Oxygen consumption ($\dot{V}o_2$) and carbon dioxide production ($\dot{V}co_2$) were also measured continuously by indirect calorimetry

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(Deltatrac, Datex Instrumentation Corp., Helsinki, Finland) and EE was recorded and calculated using a modified De Weir formula. Shivering was assessed continuously by the nurse and investigators. Arterial blood-gas tensions were measured intermittently with Stat profile (Nova Biomedical, Boston, MA, USA).

### TREATMENT DESIGN

The aim of the study was to measure the metabolic response to reduction in temperature induced by different therapeutic means. There was no randomization at enrolment of patients or of therapy sequence chosen, because the choice of treatment was decided independently by the physician in charge of the patient and not by the investigator. Three different antipyretic therapies used currently in our unit were prescribed: i.v. bolus administration of propacetamol 1000 mg or metamizol 500 mg, or external cooling with cloths plunged into iced water and placed on most of the body surface. Cloths were changed every 15–30 min. In case of failure of the first treatment, a second and, if necessary, a third treatment were given until the desired temperature was obtained. Treatment was considered to have failed if temperature either increased or decreased <1 °C in the 60 min after administration of therapy.

### METABOLIC MEASUREMENTS AND CALIBRATION

Before and after measurements, the Deltatrac metabolic monitor was calibrated for room air according to the manufacturer's instructions. Calibration for atmospheric pressure and a standard gas blend containing 95% oxygen and 5% carbon dioxide was also carried out before measurements began. The Deltatrac metabolic monitor is an open system connected to the ventilator which collects expired air from the ventilator outlet port and measures carbon dioxide and oxygen fractions in inspired, mixed expired and diluted expired gas. The carbon dioxide fractions are measured with an infrared carbon dioxide sensor (CX 104, Datex Instrumentation Corp, Helsinki, Finland); the difference between the inspired and expired oxygen fractions is measured with a differential paramagnetic oxygen sensor (OM 101, Datex Instrumentation Corp, Helsinki, Finland). $\dot{V}_{CO_2}$ is calculated as the product of the carbon dioxide fraction in the diluted expiratory flow and a constant flow of 45 litre $min^{-1}$. $\dot{V}_{O_2}$ is calculated as $\dot{V}_{CO_2}$ divided by the respiratory quotient (RQ) where $RQ=(1-F_{IO_2})/(F_{IO_2}-F_{E'O_2})/F_{E'CO_2}]-F_{IO_2}$.[5] A baseline steady state (baseline 0) was established for each patient. Steady state was defined as a stable $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and EE (<10% changes from preceding values) during at least 10 min. Thereafter, the first antipyretic therapy was given.

Before changing to alternative treatment, all variables were recorded and assumed as the new baselines (baseline 1 or 2) for the subsequent therapeutic manoeuvre. The final measurement was recorded under metabolic steady state conditions as defined above.

### STATISTICAL ANALYSIS

Data were compared between different therapies (propacetamol, metamizol and external cooling) using one-way analysis of variance; when a significant difference was seen, the Tukey–Kramer multiple comparisons test was used. The paired *t* test was also used to compare treatment effects with their respective baseline conditions. GraphPad InStat 2.0 (GraphPad Software, San Diego, CA, USA) was used for statistical analysis. Data are expressed as mean (SEM).

## Results

We studied 20 patients (four females), mean age 47 (range 17–79) yr. Admission diagnosis, treatment

*Table 1* Patient data. ARDS=Acute respiratory distress syndrome, ACB=aortocoronary bypass, Dobut=dobutamine, A=adrenaline, NA=noradrenaline, SIRS=systemic inflammatory response syndrome, D=died, S=survived

| Patient No | Age (yr)/ sex | Diagnosis | Amines | Antibiotics | APACHE score | Outcome |
|---|---|---|---|---|---|---|
| 1 | 67/M | Abdominal trauma/SIRS | — | Yes | 36 | S |
| 2 | 65/M | Aortic dissection/SIRS | — | Yes | 32 | S |
| 3 | 79/M | ARDS | — | No | 28 | S |
| 4 | 51/M | Aspiration pneumonia | — | No | 18 | S |
| 5 | 62/M | Cerebral ischaemia after ACB | — | No | 12 | S |
| 6 | 18/M | Head trauma | NA | No | 15 | S |
| 7 | 47/M | Head trauma | NA | Yes | 17 | S |
| 8 | 17/M | Head trauma | — | No | 27 | D |
| 9 | 44/M | Head trauma/aspiration pneumonia | NA | No | 19 | S |
| 10 | 72/M | Ileus/SIRS | — | No | 9 | S |
| 11 | 19/M | Multiple trauma/ARDS | — | Yes | 32 | S |
| 12 | 36/M | Multiple trauma/aspiration pneumonia | — | Yes | 5 | S |
| 13 | 22/M | Multiple trauma/septic shock | — | Yes | 19 | S |
| 14 | 30/M | Pancreatitis | — | Yes | 22 | S |
| 15 | 68/F | Perforated sigmoid colon | A | Yes | 20 | S |
| 16 | 24/M | Pneumonia | — | No | 23 | S |
| 17 | 21/M | Rhabodomyolysis, hypoxic encephalopathy | — | Yes | 32 | S |
| 18 | 56/F | SIRS after oesophageal resection | — | Yes | 23 | S |
| 19 | 61/F | Tracheo-oesophageal fistula | — | Yes | — | D |
| 20 | 71/F | Urosepsis | A, Dobut | Yes | 17 | S |

*Table 2* Individual sequences of therapy administration. If the first or the second treatment decreased fever, no other treatment was ordered. *Patient excluded from analysis (see results)

| Patient No | Treatment 1 | Treatment 2 | Treatment 3 |
|---|---|---|---|
| 1 | Propacetamol | External cooling | |
| 2 | External cooling | | |
| 3 | Metamizol | External cooling | |
| 4 | Propacetamol | Metamizol | External cooling |
| 5 | Propacetamol | Metamizol | External cooling |
| 6 | External cooling | | |
| 7 | External cooling | | |
| 8 | Propacetamol | Metamizol | External cooling |
| 9 | External cooling | | |
| 10 | Metamizol | | |
| 11 | Propacetamol | Metamizol | External cooling |
| 12 | Propacetamol | Metamizol | |
| 13 | Propacetamol | Metamizol | External cooling |
| 14 | External cooling | Metamizol | |
| 15 | External cooling | | |
| 16 | Propacetamol | Metamizol | External cooling |
| 17* | Propacetamol | External cooling | |
| 18 | Propacetamol | Metamizol | |
| 19 | Propacetamol | Metamizol | External cooling |
| 20 | Propacetamol | External cooling | |

outcome and Apache II score are listed in table 1. At the end of the study, data from one patient (No. 17) were excluded from the final analysis. This patient suffered from rhabdomyolysis and hypoxic encephalopathy and therefore received no sedation/analgesia to allow continuous neurological evaluation/surveillance. He developed an important increase in EE during external cooling (>100%) without visible signs of shivering.

Synchronized intermittent mandatory ventilation (SIMV) was used in eight patients; in 10 patients ventilation comprised pressure support mode (PS) and positive end-expiratory pressure (PEEP), and in one patient volume controlled mode was used. Only one patient (No. 7) received a neuromuscular blocking agent for controlled hyperventilation. In parallel with the decrease in body temperature, minute ventilation decreased significantly (from 14.7 (1) to 13.1 (0.9) litre $\text{min}^{-1}$; $P=0.02$), but arterial oxygen saturation ($Sa_{\text{O}_2}$ from 94 (1) % to 95 (1) %), the quotient relating arterial partial pressure of oxygen and inspired oxygen fraction ($Pa_{\text{O}_2}/FI_{\text{O}_2}$ from 203 (19) mm Hg to 190 (17) mm Hg) and arterial pH (from 7.39 (0.01) to 7.39 (0.01)) did not change significantly. Patients continuously received either enteral ($n=7$) or parenteral ($n=4$) nutrition, or a combination of both ($n=3$), or no nutritional support ($n=5$).

## METABOLIC RESULTS

Treatment sequence is shown in table 2. Fourteen patients who first received i.v. drugs needed more than one treatment to decrease body temperature. In contrast, in five of six patients external cooling significantly decreased temperature. In four patients body temperature was controlled either by metamizol ($n=2$) or by a combination of paracetamol and external cooling. Temperature, haemodynamic and metabolic variables at baseline and after treatment are shown in table 3. During baseline measurements, mean percentage of random variation was 1.8 (6.7) % (median 0.0%; lower and upper 95% confidence intervals −2.3% and +5.8%, respectively). There were no differences between baselines 0, 1 and 2 for all study variables. Temperature did not change significantly after administration of propacetamol. Metamizol resulted in a statistically significant but clinically irrelevant decrease in temperature from 38.9 (0.2) to 38.5 (0.3) °C ($P=0.02$). In contrast, application of external cooling decreased temperature from 39.1 (0.2) to 37.1 (0.2) °C ($P<0.0001$). There were no clinical signs of shivering with either therapy.

Treatment with metamizol or external cooling decreased heart rate significantly ($P=0.0043$ and $P<0.0001$, respectively), but no significant change was observed after administration of propacetamol ($P=0.14$).

Five patients received vasopressor infusions to maintain adequate systemic arterial pressure, and in three (Nos 6, 7 and 15) the dose of these agents was reduced during the study. In two other patients (Nos 9 and 20) no change in noradrenaline infusion was made. Table 3 demonstrates that excluding the three patients in whom the catecholamine dose was modified did not significantly influence the metabolic changes induced by the different treatments.

Administration of propacetamol and metamizol did not significantly change mean values of EE ($P=0.35$ and $P=0.41$, respectively). However,

*Table 3* Haemodynamic and metabolic variables at baseline and after treatment (mean (SEM)). EE=energy expenditure, HR=heart rate, MAP=mean arterial pressure, T=temperature, $\dot{V}\text{O}_2$=oxygen consumption, $\dot{V}\text{CO}_2$=carbon dioxide production. †Three patients were excluded after i.v. catecholamine dose adjustment (see results). *$P<0.05$, ***$P<0.0001$ compared with baseline

| Method | | T (°C) | HR (beat $\text{min}^{-1}$) | MAP (mm Hg) | EE (kcal $\text{day}^{-1}$) | $\dot{V}\text{O}_2$ (ml $\text{min}^{-1}$) | $\dot{V}\text{CO}_2$ (ml $\text{min}^{-1}$) |
|---|---|---|---|---|---|---|---|
| Propacetamol | Baseline | 39.2 (0.2) | 117 (5) | 79 (5) | 1974 (76) | 286 (13) | 258 (14) |
| ($n=11$) | After treatment | 39.2 (0.2) | 114 (5) | 79 (5) | 2009 (85) | 287 (12) | 260 (16) |
| | % Baseline | | | | 1.8 (1.8) | 0.6 (2.1) | 0.6 (1.8) |
| Metamizol | Baseline | 38.9 (0.2) | 118 (4) | 79 (4) | 2006 (90) | 285 (13) | 262 (14) |
| ($n=12$) | After treatment | 38.5 (0.3)* | 112 (4)* | 79 (5) | 1946 (109) | 282 (17) | 254 (14) |
| | % Baseline | | | | −2.9 (4.0) | −1.2 (4.5) | 3.0 (1.7) |
| External cooling | Baseline | 39.1 (0.2) | 110 (4) | 84 (4) | 2034 (73) | 297 (11) | 252 (10) |
| ($n=16$) | After treatment | 37.1 (0.2)*** | 96 (5)*** | 85 (4) | 1791 (88)* | 259 (12)* | 226 (15)* |
| | % Baseline | | | | −11.9 (3.5) | −12.6 (3.3) | −10.9 (4.3) |
| External cooling† | Baseline | 39.2 (0.3) | 113 (7) | 84 (5) | 2058 (82) | 301 (13) | 255 (12) |
| ($n=13$) | After treatment | 37.2 (0.2)*** | 99 (8)*** | 86 (5) | 1839 (138)* | 265 (19)* | 235 (21)* |
| | % Baseline | | | | −10.4 (4.0) | −11.6 (3.9) | −8.6 (4.7) |

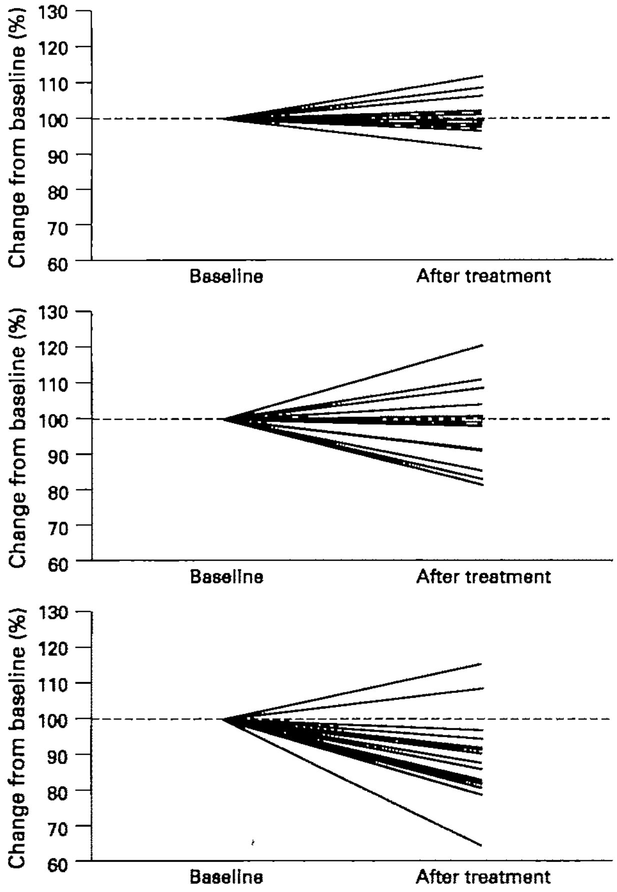

*Figure 1* Individual variations in energy expenditure. Post-treatment values for propacetamol (top), metamizol (middle) and external cooling (bottom) are expressed as percentage of baseline.

external cooling decreased EE significantly from 2034 (73) to 1791 88 kcal day$^{-1}$ ($P$=0.004). Metabolic variations calculated as percentage changes from baseline are summarized in table 3. Mean $\dot{V}\mathrm{O}_2$ decreased by 12.6 (3.3) % and $\dot{V}\mathrm{CO}_2$ by 10.9 (4.3) % during external cooling.

Figure 1 shows individual percentage variation in EE from baseline for treatment with propacetamol, metamizol and external cooling. There was wide variability among patients' responses to the treatments with propacetamol and metamizol. However, in patients treated with external cooling, EE decreased by 6.1–36% from baseline in 17 patients; in two patients (Nos 14 and 13) EE increased by 7.9% and 15.3%, respectively.

## Discussion

Twenty febrile ICU patients were prospectively enrolled to compare the respective effects of antipyretic drugs (propacetamol or metamizol) or physical (external cooling) therapies on body temperature and metabolic variables using indirect calorimetry. The major finding was a decrease in EE related to a decrease in body temperature in patients treated by external cooling, whereas treatment by propacetamol or metamizol did not induce a clinically relevant decrease in body temperature.

External cooling is thought to have no effect on the thermoregulatory setpoint.[6–8] Furthermore, it is generally admitted that a physiological response to cold stress is shivering[2] to maintain core temperature. Therefore, in response to external cooling, EE could either vary independently of T° or increase with diminution of body temperature. Our findings did not confirm our hypothesis that external cooling did not affect or increase metabolic rate. The association between a decrease in both body temperature and EE could be because of the absence of a compensatory homeostatic response. This physiological response was most probably blunted by morphine or sedation with midazolam, or both.[9–12] This possibility is fully supported by the fact that patient No. 17 was excluded because he developed a shivering-equivalent reaction with increased EE while not receiving opioids as he required close neurological surveillance. This observation further supports our hypothesis that in the absence of sedation or analgesia, increased EE is expected during external cooling. A similar observation was also reported by Manthous and colleagues.[3] Indeed, shivering is suppressed by general anaesthetics, centrally acting agents such as clonidine and especially by opioids such as pethidine, morphine and fentanyl.[10]

In clinical practice, although controversial, antipyretic therapy is often prescribed to combat temperatures greater than 38.5 °C. Indeed, fever complements the host immunological defence against invasion by micro-organisms. However, when a decrease in body temperature seems clinically important then paracetamol or metamizol are often prescribed. Drug-induced antipyrexia is preferred because it is easier than application of iced sponges and has proved to be efficient in paediatric studies.[13–15] Our study has demonstrated that external cooling, under sedation–analgesia conditions, is a valuable means of decreasing temperature with a concomitant decrease in oxygen consumption. The 12% decrease in oxygen consumption in externally cooled patients matched previously published data reporting a 5–7% change in metabolism per 1 °C change in temperature.[16] Thus even though the benefit of decreasing fever is debatable, decreasing EE and oxygen consumption may be clinically relevant in patients lacking coronary artery oxygen delivery reserve experiencing a septic episode or severely hypoxaemic.

The limitations of the study are that first, the treatment sequence was not randomized, but the physician in charge of the patient was proposed a random sequence of treatment by the investigators and the final decision left to him. This procedure may have introduced possible bias into the study. Second, to minimize spontaneous changes in body temperature not related to the treatment procedure, there was no washout period between i.v. drug administrations, which may have resulted in some overlapping between treatments. However, from a clinical viewpoint, if 2 h after administration of treatment no clinically relevant effect is observed, then therapy is usually considered to have failed, leading to administration of another form of therapy. Finally, these effects were not caused by variations in pH, nutrition or ventilation, or by changes in sedation or analgesia (tables 2, 3).

We conclude that propacetamol and metamizol administration had no observable effect on fever in critically ill patients under analgesia and sedation, whereas external cooling efficiently decreased body temperature and metabolic demands.

## Acknowledgements

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# Hormonal responses and cardiac filling pressures in head-up or head-down position and pneumoperitoneum in patients undergoing operative laparoscopy

E. A. HIRVONEN, L. S. NUUTINEN AND O. VUOLTEENAHO

## Summary

In order to determine if there are differences in stress responses, as reflected in neuroendocrine activation, we have compared data from two groups of patients undergoing laparoscopic surgery either in the head-up position for cholecystectomy or in the head-down position for hysterectomy. Arterial blood samples were obtained for measurement of serum concentrations of cortisol, catecholamines, renin activity and atrial natriuretic peptide (measured as *N*-terminal peptide of proANP), and haemodynamic data (pulmonary capillary wedge pressure, PCWP) were collected at the following times: in awake patients, supine at rest (baseline); in awake patients in the position used during surgery; during laparoscopy; and 2 h after surgery. The same anaesthetic technique and normocapnic mechanical ventilation were used in both groups. There were no significant differences between groups in cortisol or adrenaline concentrations, or in renin activity. There was, however, a threefold increase in cortisol towards the recovery period in both groups. Noradrenaline concentrations increased more in the head-up group suggesting increased sympathetic nervous activity. In awake patients, plasma NT-proANP concentrations were significantly higher in the head-down tilt compared with the head-up position, and NT-proANP correlated well with PCWP. During pneumoperitoneum, however, NT-proANP concentrations remained low in spite of increased PCWP suggesting that inflation of the abdomen interferes with venous return. In conclusion, abdominal surgical laparoscopy in both the head-up and head-down positions caused marked activation of neuroendocrine responses. The two surgical positions, however, differed in their effect on the circulation. In awake patients, head-down tilt was associated with increased concentrations of plasma NT-proANP, indicating increased venous return and atrial stretch. (*Br. J. Anaesth.* 1997; **78**: 128–133)

**Key words**
Surgery, hormonal response. Hormones, adrenal. Hormones, atrial natriuretic peptide. Position, effects. Surgery, laparoscopy. Cardiovascular system, effects.

Nociceptive surgical stimulation is accompanied by activation of the hypothalamic–pituitary–adrenal (HPA) axis and by increased activity of the sympathetic nervous system, which is generally referred to as the stress response to surgery. It is believed commonly that the magnitude of the response is related directly to the size of the wound.[1] On the basis of clinical experience, minimal-access techniques in abdominal surgery are associated with less postoperative stress than conventional surgery. Recent reports concerning laparoscopic cholecystectomy have, however, indicated that the stress response, as measured by intraoperative release of cortisol and catecholamines, is not diminished by the laparoscopic approach and may even be increased in comparison with the open technique.[2–5] The stress response to surgery can be modified by anaesthesia,[6] surgical positioning[7] and probably by the site of the operation.[8]

Three major neurohumoral systems are involved in maintaining arterial pressure and circulating volume: sympathetic nervous system, renin–angiotensin–aldosterone system (RAA) and the vasopressin system.[9 10] These vasopressor systems are counterbalanced by atrial natriuretic peptide (ANP) in the regulation of circulating volume and arterial pressure.[11 12] The major stimulus for ANP secretion from the atrium is atrial stretch caused by increased atrial transmural pressure.[13] An increase in atrial cavity pressure without an increase in atrial transmural pressure (as with cardiac tamponade) does not trigger ANP release.[13] During laparoscopic procedures, creation of pneumoperitoneum increases right and left atrial intraluminal pressures.[14–16] There are conflicting views on whether or not increased central pressures represent increased central blood volume or increased intrathoracic pressure caused by pneumoperitoneum.[14–16]

The neuroendocrine responses to upper and lower abdominal operative laparoscopy have not been compared. Although similar, the two have significant procedural differences. The first aim of this study

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therefore was to determine if neuroendocrine responses associated with upper and lower abdominal laparoscopy have clinically relevant differences. Second, we examined the correlation between changes in cardiac filling pressures and release of ANP.

## Patients and methods

The study was approved by the Ethics Committee of Kuopio University Hospital and Kuopio University, and written informed consent was obtained from each patient. We studied 16 ASA I–II patients undergoing elective laparoscopic cholecystectomy (LC group) and 19 ASA I–II patients undergoing elective laparoscopic hysterectomy (LH group). Patients with significant cardiovascular, hepatic or renal disease, and those using some angiotensin converting enzyme inhibitors were excluded.

All patients were premedicated with diazepam 10–15 mg orally. Patients also received their usual morning medication, if any, except diuretics. After transfer to the operating theatre, i.v. infusion of 0.9% NaCl solution was started at a rate of 5 ml $kg^{-1}$ $h^{-1}$ for 1 h and continued at a rate of 2.5 ml $kg^{-1}$ $h^{-1}$ thereafter. A radial artery cannula and a 7.5-French gauge thermodilution pulmonary artery catheter for haemodynamic measurements and blood sampling were introduced under local anaesthesia. Mean arterial pressure (MAP), mean central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP) and cardiac output (CO) were recorded by a haemodynamic monitor (AS/3, Datex Corp., Finland). The monitor calculated cardiac index (CI=CO/body surface area) and systemic vascular resistance index (SVRI=(MAP−CVP)×80/CI). The pressure transducers were located at the level of the right atrium. Haemodynamic data were collected simultaneously with blood sampling.

### ANAESTHESIA AND SURGERY

The same anaesthetic technique was used in all patients. Anaesthesia was induced with glycopyrronium 0.004 mg $kg^{-1}$, diazepam 2.5–10 mg, thiopentone (mean 3.9 mg $kg^{-1}$), fentanyl 0.1 mg and vecuronium 0.1 mg $kg^{-1}$. After tracheal intubation, general anaesthesia was maintained with up to 1 MAC of isoflurane and 35% oxygen in an oxygen–air mixture. Additional doses of fentanyl 0.05–0.1 mg and vecuronium 1–2 mg were given when needed. An extra i.v. infusion of colloid solution (6% hydroxyethyl-amylopectinase, Plasmafusin, Pharmacia) in 250-ml doses up to 500 ml was given if PCWP was less than 4 mm Hg before laparoscopy. During anaesthesia minute ventilation was adjusted to maintain end-tidal $P\text{CO}_2$ at 4.5–5.0 kPa by controlled mechanical ventilation. Pneumoperitoneum for laparoscopy was produced with a Verres' needle using a carbon dioxide insufflator, and intra-abdominal pressure was maintained automatically at the desired level (13–16 mm Hg, recorded by the insufflator). All operations were performed successfully by the laparoscopic approach. Six hysterectomy patients experienced haemorrhage (more than 200 ml) during operation (range 300–1000 ml). Blood loss was replaced with 6% hydroxyethyl-amylopectinase (Plasmafusin, Pharmacia) and red blood cells. During the first 2 h in the recovery room, fentanyl 0.05 mg i.v. was administrated for pain when needed.

### BLOOD SAMPLING

Baseline arterial blood samples were obtained approximately 30 min after catheterization with the patient resting in bed (baseline). Subsequent awake samples were obtained at 5 min after placing the patient on the operating table to the position used during laparoscopy: 15–20° head-up for cholecystectomy or 25–30° head-down for hysterectomy. Blood samples during surgery were obtained at the end of laparoscopy before desufflation of the intra-abdominal gas and with the patient still in the head-up or head-down position. Postoperative blood samples were obtained 2 h after surgery in the recovery room.

### ASSAYS

Blood for adrenaline and noradrenaline assays was collected in ice-chilled vacuum tubes containing glutathione and ethylene-glutamine-tetra-acetic acid, for renin and NT-proANP assays in ice-chilled tubes containing EDTA, and for cortisol measurements in plain serum tubes. Samples for plasma separation were centrifuged within 10 min and stored at −20 °C (for catecholamine assays at −70 °C) until analysed. Blood samples for cortisol measurement were handled as above after clotting.

Adrenaline and noradrenaline concentrations in plasma were analysed by high performance liquid chromatography with coulometric detection, as described in detail elsewhere.[17] The detection limits of adrenaline and noradrenaline were 0.1 nmol $litre^{-1}$ and 0.075 nmol $litre^{-1}$, respectively. Intra- and inter-assay coefficients of variations (cv) for adrenaline were 11% and 11% at 0.26 nmol $litre^{-1}$ and for noradrenaline, 7.8% and 15.2% at 1.42 nmol $litre^{-1}$, respectively. The normal ranges for adrenaline and noradrenaline are 0.32 (0.19) nmol $litre^{-1}$ and 0.98 (0.27) nmol $litre^{-1}$, respectively. Cortisol concentrations in serum were determined with a commercially available direct radioimmunoassay (Orion Diagnostica Cortisol [$^{125}$I], Orion Co, Turku, Finland). The sensitivity of the method (the smallest detectable concentration) is approximately 4–7 nmol $litre^{-1}$, the intra-assay cv is 2.1–4.1% and the inter-assay cv is 4.3–9.0% within the measurement range; the normal range for morning concentrations is 150–650 nmol $litre^{-1}$. Plasma renin activity was measured with the Medix Angiotensin I Test (Medix Biochemica Corporation, Kauniainen, Finland). The detection limit of the assay was <0.2 μg $litre^{-1}$ $h^{-1}$ (normal range 0.9–2.0 μg $litre^{-1}$ $h^{-1}$). Intra- and inter-assay cv were 15.4% and 7.7% at 1.0 μg $litre^{-1}$ $h^{-1}$, 8.9% and 5.6% at 3.3 μg $litre^{-1}$ $h^{-1}$, and 8.7% and 2.6% at 7.8 μg $litre^{-1}$ $h^{-1}$, respectively.

NT-proANP was assayed directly from plasma as follows. Standards and samples (25 µl) in duplicate were incubated with 200 µl of radioiodinated NT-proANP and 200 µl of rabbit anti-human NT-proANP antiserum (final dilution 1/40 000) overnight at +4 °C. Bound and free fractions were separated by double antibody precipitation in the presence of polyethylene glycol. The sensitivity of the assay was 0.75 fmol/tube, the inter-assay cv was 5.3% at 0.275 nmol litre$^{-1}$ and 9.3% at 0.128 nmol litre$^{-1}$. The antiserum cross reacts fully with proANP$_{1\text{-}126}$ and proANP$_{1\text{-}98}$ but does not recognize ANP (proANP$_{99\text{-}126}$), B-type natriuretic peptide or C-type natriuretic peptide (cross reaction <0.01%).[18] Basal plasma concentration of NT-proANP in healthy adults is 0.355 (0.123) nmol litre$^{-1}$.

### STATISTICAL ANALYSIS

Results are expressed as mean (SEM), except patient data, which are given as mean (SD) and range. Correlations between variables are reported by the Pearson correlation coefficients. All statistical analyses were performed with a statistical software package (SPSS/PC+, SPSS Inc., Chicago, IL, USA). Data were analysed by one- and two-way analysis of variance for repeated measurements. Statistically significant differences were isolated by means of the paired Student's *t* test (within group) and by the unpaired Student's *t* test (between groups). The relationships between NT-proANP and CVP, and between NT-proANP and PCWP were studied by linear regression analysis. The level of significance was $P<0.05$ unless otherwise indicated.

## Results

There were no significant differences in patient characteristics between the laparoscopic cholecystectomy (LC) and laparoscopic hysterectomy (LH) groups (table 1). Laparoscopy was more prolonged in the LH group than in the LC group.

There were no significant differences between the two groups in any of the hormones measured under awake baseline conditions (fig. 1). Noradrenaline concentration increased both in the head-up and head-down positions. The decrease in NT-proANP in the head-up position and the increase in NT-proANP in the head-down position were not significant compared with baseline, but the difference between the LC and LH groups was significant ($P=0.006$).

Laparoscopy with carbon dioxide pneumoperitoneum increased serum cortisol to concentrations more than two times higher than those detected before surgery. Plasma noradrenaline increased in both groups, but concentrations were significantly higher in the LC group than in the LH group

*Table 1* Patient characteristics and duration of laparoscopy, surgery and anaesthesia (mean (SD) [range])

| | Cholecystectomy group | Hysterectomy group | *P* (between groups) |
|---|---|---|---|
| Age (yr) | 45 [19–69] | 44 [32–69] | ns |
| Weight (kg) | 71 9 (11.0) [55–91] | 67.0 (10.3) [49–86] | ns |
| Height (cm) | 163 (5.5) [152–171] | 163 (5.4) [152–173] | ns |
| Body surface area (m$^2$) | 1.77 (0.14) [1 56–1.97] | 1.72 (0.15) [1 45–1.99] | ns |
| Body mass index (kg m$^{-2}$) | 26.9 (3.8) [20–33] | 24.9 (2 8) [19–31] | ns |
| Duration of laparoscopy (min) | 82 (15) [58–118] | 105 (25) [61–142] | <0.002 |
| Duration of operation (min) | 99 (16)[71–135] | 148 (32) [89–213] | <0.001 |
| Duration of anaesthesia (min) | 140 (19) [115–175] | 196 (36) [122–257] | <0.001 |

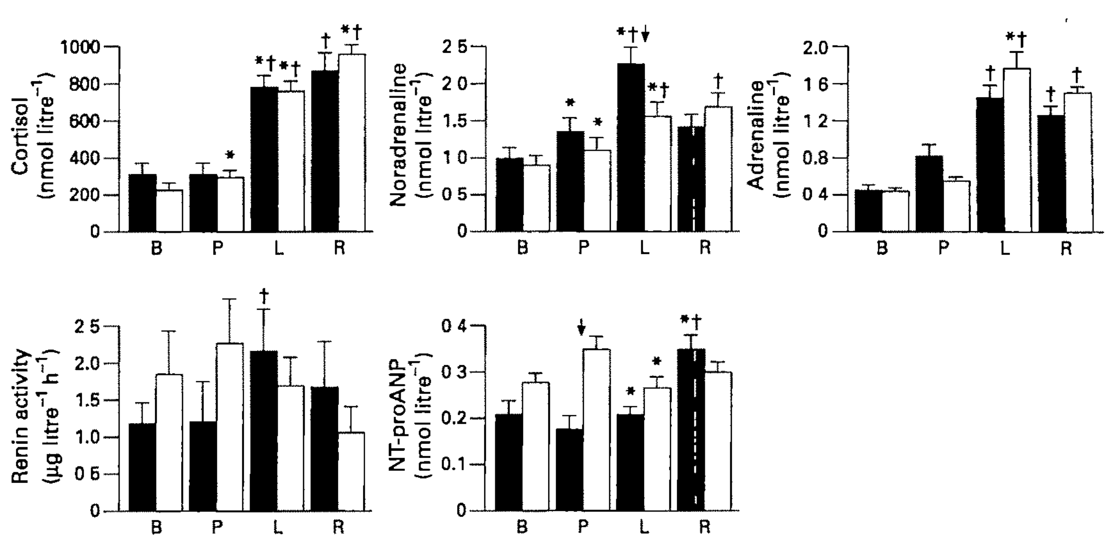

*Figure 1* Mean (SEM) plasma concentrations of adrenaline, noradrenaline, cortisol and NT- proANP, and renin activity in laparoscopic cholecystectomy (■) and laparoscopic hysterectomy (□) patients at baseline (B), during awake head-up or head-down positioning (P), during laparoscopy (L) and during recovery (R). The arrows indicate significant differences between the cholecystectomy and hysterectomy groups *$P<0.05$ compared with previous values, †$P<0.05$ compared with baseline values.

*Table 2* Haemodynamic data in patients undergoing laparoscopic cholecystectomy or laparoscopic hysterectomy. MAP=mean arterial pressure; CI=cardiac index; SVRI=systemic vascular resistance index; PCWP=pulmonary capillary wedge pressure; CVP=central venous pressure. Results are given as mean (SEM). *$P<0.05$ compared with baseline condition

| | Awake, baseline | Awake, head-up or head-down | Laparoscopy | Recovery |
|---|---|---|---|---|
| Laparoscopic cholecystectomy | | | | |
| MAP (mm Hg) | 94 (3.1) | 99 (3.1)* | 94 (3.1) | 96 (3.1) |
| CI (litre $min^{-1}$ $m^{-2}$) | 3.39 (0.16) | 3.12 (0.16)* | 2.77 (0.19)* | 4.04 (0.25)* |
| SVRI (dyn s $cm^{-5}$ $m^{-2}$) | 2170 (107) | 2620 (182)* | 2648 (193)* | 1863 (122)* |
| PCWP (mm Hg) | 7.6 (0.8) | 3.7 (0.8)* | 7.1 (0.6) | 10.4 (0.8)* |
| CVP (mm Hg) | 4.4 (0.6) | 1.1 (0.6)* | 7.1 (0.8)* | 6.3 (0.5)* |
| Laparoscopic hysterectomy | | | | |
| MAP (mm Hg) | 104 (3.7) | 111 (3.8)* | 96 (2.6)* | 92 (3.5)* |
| CI (litre $min^{-1}$ $m^{-2}$) | 3.83 (0.19) | 3.61 (0.18)* | 2.71 (0.11)* | 3.81 (0.19) |
| SVRI (dyn s $cm^{-5}$ $m^{-2}$) | 2128 (139) | 2376 (156)* | 2550 (159)* | 1900 (122)* |
| PCWP (mm Hg) | 9.4 (0.7) | 14.1 (1.0)* | 12.5 (1.1)* | 8.4 (1.0) |
| CVP (mm Hg) | 5.4 (0.5) | 9.4 (0.7)* | 11.9 (0.8)* | 4.3 (0.7) |

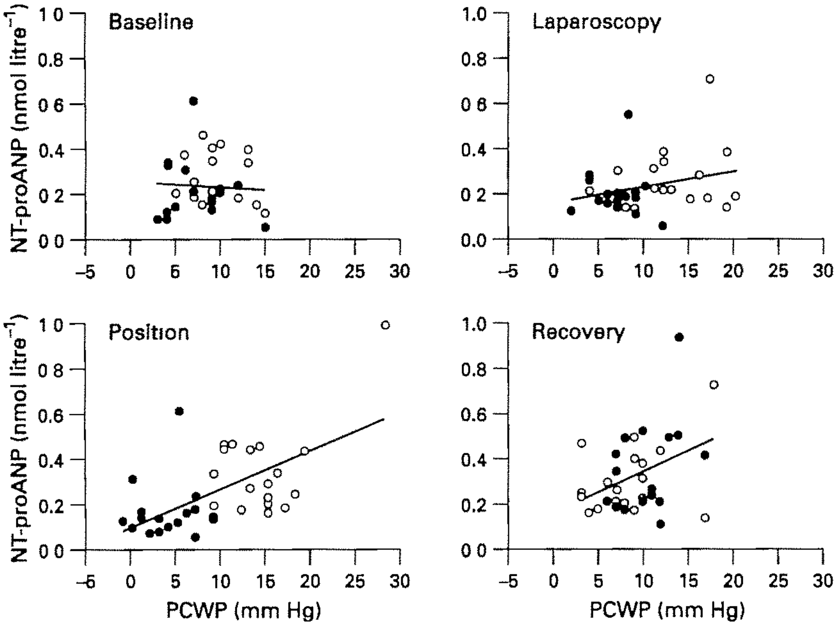

*Figure 2* Correlations and linear relationship between pulmonary capillary wedge pressure (PCWP) and NT-proANP concentrations at baseline, during awake head-up or head-down positioning (position), during laparoscopy and during recovery in the cholecystectomy (●) and hysterectomy (○) patients. Line fit by method of least squares.

($P=0.02$). Plasma adrenaline increased in both groups, but plasma renin activity (PRA) increased only in the LC group during laparoscopy compared with baseline. Plasma NT-proANP concentrations were higher in the LC group and lower in the LH group during laparoscopy compared with awake values in the same surgical position. NT-proANP concentrations during laparoscopy were not significantly different from baseline awake concentrations.

At 2 h after surgery, serum cortisol concentrations increased further from laparoscopic concentrations in the LH group. Plasma adrenaline concentrations were still above baseline in both groups. In the LH group plasma noradrenaline concentrations were increased above baseline, but in the LC group they had returned to near baseline. Plasma NT-proANP concentrations were increased above laparoscopic and baseline concentrations after surgery in the LC group ($P=0.01$).

MAP and SVRI increased, and cardiac index (CI) decreased, both in the head-up and head-down positions in awake patients (table 2). PCWP and CVP decreased in the head-up position and increased in the head-down position. During laparoscopy, CI decreased and SVRI increased compared with baseline in both groups. Pneumoperitoneum increased PCWP and CVP in head-up laparoscopy, but in head-down laparoscopy only CVP increased further compared with the same position in awake patients. During recovery, most of the values approached baseline, although CI, PCWP and CVP remained increased in the LC group.

For all patients grouped together ($n=35$), linear correlations between NT-proANP and PCWP were poor under baseline conditions ($r=0.06$, $P=0.75$)

and during laparoscopy ($r$=0.27, $P$=0.11). However, during awake head-up or head-down positions and during recovery, correlations were significant ($r$=0.60, $P$=0.0002, and $r$=0.40, $P$=0.017, respectively). Similar correlations (with slightly lower $r$ values) were found between NT-proANP and CVP, with correlation coefficients of 0.04, 0.27, 0.48, and 0.32 at baseline, during laparoscopy, during awake head-up or head-down positions and during recovery, respectively. The possible effect of blood loss in the LH group on NT-proANP values during laparoscopy and recovery was examined, and no significant correlations were found ($P$=0.79, $P$=0.44).

Figure 2 shows the linear correlations between NT-proANP and PCWP during the different phases of the study.

## Discussion

We have demonstrated that laparoscopy either in the head-up position during cholecystectomy or in the head-down position during hysterectomy caused marked activation of neuroendocrine responses, reflected by increases in serum cortisol and plasma catecholamine concentrations. We found no significant differences between upper and lower abdominal surgical laparoscopy in serum cortisol or plasma adrenaline concentrations or in plasma renin activity. Plasma noradrenaline concentrations were significantly higher in the cholecystectomy patients which may not be an unexpected result considering the prominent sympathetic sensory innervation of the upper abdomen. Varying the surgical position may also have contributed to the difference. Head-down tilt compared with the supine position during lower abdominal surgery has been reported to be associated with decreased sympathetic nervous system activity and lower plasma noradrenaline concentrations.[7] Further, higher noradrenaline secretion has generally been found in the upright compared with the supine position in awake volunteers.[19]

NT-proANP is secreted from the heart in equimolar quantities with the biologically active ANP. It is, however, a much more stable peptide in the circulation than ANP, which is eliminated rapidly from blood by receptor binding and enzymatic degradation.[18] The close correlation between NT-proANP and ANP has been demonstrated previously in patients with cardiac disease.[20 21] Stretch of cardiac atria is the most potent stimulus for the ANP system, and PCWP and CVP have been shown to correlate positively with release of natriuretic peptides from the atria.[20 22] Our results, however, showed that during pneumoperitoneum there was a poor correlation between the activity of the ANP system, as reflected by plasma NT-proANP concentrations, and measured intraluminal cardiac filling pressures, reflected by PCWP and CVP. The unchanged NT-proANP concentrations, in spite of increased filling pressures during pneumoperitoneum, indicate the surprising conclusion that atrial transmural pressures do not increase during the procedure. Inflation of the abdomen associated with the laparoscopic technique may interfere with venous return, thus counteracting the increase in central blood volume otherwise resulting from the head-down tilt.

Plasma ANP concentrations have been shown to decrease or remain stable after severe blood loss in animals.[23 24] In contrast, moderate blood loss (up to 1000 ml) in healthy volunteers did not induce significant decreases in ANP release.[25] Some patients in our hysterectomy group experienced haemorrhage up to 1000 ml. Blood loss was replaced with colloid solutions and red blood cells, and the continuously monitored patients did not show signs of hypovolaemia at any phase of the study.

Despite the fact that the magnitude of the neuroendocrine response appeared to be correlated directly with the extent of the surgical wound[1] and that minimal access techniques appeared to cause less postoperative stress than conventional surgery, intraoperative increases in circulating cortisol and catecholamine concentrations have been shown to be similar[2–4] or even larger[5] with the laparoscopic compared with the open technique. Cooper and co-workers showed that even short-duration gynaecological laparoscopy produced significant hormonal and glycaemic responses.[26] This is in keeping with our results in which both upper and lower abdominal laparoscopic surgery were associated with clear activation of the HPA axis and the catecholamine system.

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# Effects of clonidine on the pituitary hormonal response to pelvic surgery

F. M. LYONS, S. BEW, P. SHEERAN AND G. M. HALL

## Summary

We have investigated the effects of the central $\alpha_2$ adrenoreceptor agonist, clonidine, given i.v. before induction of anaesthesia, on the haemodynamic and endocrine responses to pelvic surgery. Twenty patients were allocated randomly to receive either clonidine 3 $\mu$g kg$^{-1}$ or an equivalent volume of 0.9% sodium chloride solution. Arterial pressure, heart rate, and circulating concentrations of cortisol, growth hormone, glucose and lactate were measured during and in the 24 h after total abdominal hysterectomy. Arterial pressure and heart rate decreased significantly in the clonidine group during surgery and in the early postoperative period. There were no differences between groups in serum cortisol or growth hormone concentrations throughout the study. Despite an effective decrease in the cardiovascular response to surgery, clonidine 3 $\mu$g kg$^{-1}$ i.v. had no significant effect on pituitary hormone secretion. (*Br. J. Anaesth.* 1997; **78**: 134–137)

**Key words**

Hormones, glucocorticoid. Hormones, growth. Surgery, gynaecological. Surgery, hormonal response. Sympathetic nervous system, clonidine. Metabolism, glucose.

The antihypertensive drug clonidine is a centrally acting $\alpha_2$ agonist.[1] It is useful as a premedicant because of its sedative, anxiolytic and analgesic effects. Clonidine decreases the amount of isoflurane and fentanyl needed to supplement general anaesthesia and may offer myocardial protection to patients with cardiovascular disease.[2,3] Recognized neuroendocrine effects of clonidine include inhibition of sympathoadrenal activity with decreased circulating catecholamine concentrations,[4,5] decreased secretion of adrenocorticotrophic hormone (ACTH) and cortisol,[6] and decreased secretion of insulin and enhanced growth hormone release (GH).[7,8] After i.v. administration of clonidine, the maximum effect occurs within 60–90 min and the terminal elimination half-life is in the range 20–25 h.[9,10]

Two studies have examined the effects of oral premedication with clonidine on the early haemodynamic and endocrine changes associated with surgery. One study investigated neurosurgical patients and showed a decrease in the cortisol response with clonidine.[11] The other showed that clonidine added to diazepam premedication, compared with diazepam alone, did not alter the cortisol and GH response to surgery.[12] The purpose of this study was to examine the effects of preoperative i.v. clonidine on the haemodynamic and endocrine responses, during and in the 24 h after pelvic surgery.

## Patients and methods

Approval for the study was obtained from the local Ethics Committee for clinical research (reference No. 94.05.17). Written informed consent was obtained from each patient .

We studied 20 patients with benign disease undergoing total abdominal hysterectomy. Patients had no history of endocrine or cardiovascular disease. They were allocated randomly using sealed envelopes to receive either clonidine ($n=10$) or 0.9% sodium chloride (NaCl) solution ($n=10$) i.v. before induction of anaesthesia. Previous work indicated that a sample size of 20 patients had a power of 90% to detect a standardized difference of 1.5 in heart rate and systolic arterial pressure, at a significance level of 5%.

Patients did not receive premedication. On arrival in the anaesthetic room an i.v. cannula was inserted for drug administration. Non-invasive monitoring of heart rate, arterial pressure and arterial oxygen saturation was commenced. A central venous catheter was inserted, via the antecubital fossa, for fluid administration and blood sampling. Baseline measurements of heart rate, arterial pressure and arterial oxygen saturation were recorded, and a blood sample was obtained for measurement of circulating hormones and metabolites. Patients then received either clonidine 3 $\mu$g kg$^{-1}$ in 0.9% NaCl solution 20 ml or 0.9% NaCl solution 20 ml , i.v. over 15 min.

General anaesthesia was induced in all patients with fentanyl 4 $\mu$g kg$^{-1}$ and a sleep dose of thiopentone. Vecuronium 0.1 mg kg$^{-1}$ was used to facilitate

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tracheal intubation. Anaesthesia was maintained with 0.5–1.5% isoflurane and 60% nitrous oxide in oxygen. Mean end-tidal isoflurane concentrations were 0.6 (SEM 0.1) % in the clonidine group and 0.7 (0.1) % in the saline group. All patients received 0.9% NaCl 6 ml kg$^{-1}$ h$^{-1}$ in the intraoperative period and 2 ml kg$^{-1}$ h$^{-1}$ after operation as i.v. maintenance fluid. Blood losses were replaced with an equivalent volume of Gelofusin. After operation, patients received patient-controlled analgesia with morphine.

Blood samples were obtained and cardiovascular measurements made at the following times: before administration of placebo or clonidine, at skin incision (0 h) and at 1, 2, 4, 6, 12 and 24 h after skin incision. All samples were analysed in duplicate for blood glucose and lactate concentrations by methods described previously.[13] Serum concentrations of cortisol and GH were measured with commercially available enzyme linked immunoassay kits. The sensitivity of the assay was 7.3 nmol litre$^{-1}$ for cortisol (Milenia Cortisol EIA) and 0.11 miu litre$^{-1}$ for growth hormone (Medgenix-HGH-EASIA). Intra-assay coefficients of variation were 3.2% for cortisol and 2.1% for GH; inter-assay coefficients of variation were 8% for cortisol and 7% for GH. Packed cell volume (PCV) was measured using a microcapillary method. The investigator undertaking the analysis was unaware of the identity of the sample.

Statistical analysis was undertaken using Statview SE+ Graphics computer software (Abacus concepts, Berkeley, CA, USA). GH values were not distributed normally and are shown as median (range); values below the sensitivity of the GH assay were ascribed that value. All other hormonal, metabolic and cardiovascular variables are presented as mean (SEM). Differences within groups with respect to baseline samples were assessed by two-way analysis of variance with Dunnet's test, and between-group differences by one-way analysis of variance. GH data were analysed using Friedman's two-way analysis of variance and the Kruskal–Wallis test for differences between groups. $P<0.05$ was accepted as significant.

## Results

The groups were similar in mean age (control 44 (range 36–52) yr, clonidine 46 (37–64) yr), body weight (control 66 (55–82) kg, clonidine 67 (60–86) kg), duration of surgery (control 80 (50–110) min, clonidine 75 (40–110) min) and 24-h morphine consumption (control 46 (19–87) mg, clonidine 54 (33–76) mg). Two patients received atropine 0.3 mg i.v. for bradycardia (heart rate ≤45 beat min$^{-1}$).

### CARDIOVASCULAR CHANGES

Heart rate was unchanged throughout the study in the control group from the baseline value of 80 beat min$^{-1}$. In the clonidine group, heart rate decreased significantly from the baseline value of 78 beat min$^{-1}$ until 4 h after operation ($P<0.05$). There was a significant difference in heart rate between the groups at skin incision ($P<0.01$), and at 1 and 2 h ($P<0.05$).

Systolic arterial pressure decreased significantly from baseline at skin incision and at 4 h ($P<0.05$) in the control group. In the clonidine group, systolic pressure decreased significantly from baseline at skin incision and at 1, 2, 4, 6 ($P<0.01$) and 12 h ($P<0.05$). There was a significant difference in systolic arterial pressure between the groups at skin incision ($P<0.01$), and at 1 and 2 h ($P<0.05$).

Diastolic arterial pressure did not change from baseline in the control group throughout the study. In the clonidine group, diastolic pressure decreased significantly from baseline at skin incision, 1 h ($P<0.01$) and 4 h ($P<0.05$). There was a significant difference between groups at skin incision ($P<0.01$) and at 2 h ($P<0.05$).

### CIRCULATING HORMONES AND METABOLITES (TABLE 1)

Serum concentrations of cortisol increased significantly from a baseline value of 603 nmol litre$^{-1}$ at 1, 2, 4 and 6 h ($P<0.05$) in the control group, and

*Table 1* Mean (SEM) blood glucose, blood lactate, and serum cortisol concentrations and packed cell volume (PCV) Growth hormone concentrations are presented as median (range). Within group differences· *$P<0$ 05; ** $P<0.01$. B=Baseline

| | B | 0 h | 1 h | 2 h | 4 h | 6 h | 12 h | 24 h | Control *vs* clonidine |
|---|---|---|---|---|---|---|---|---|---|
| Blood glucose (mmol litre$^{-1}$) | | | | | | | | | |
| Control | 4 3 (0.4) | 5.4 (0.4) | 5.3 (0.3) | 6.6** (0 5) | 6 2* (0.4) | 5.9* (0.3) | 6 2* (0.5) | 5.2 (0.4) | $P<0.05$ |
| Clonidine | 4.3 (0.2) | 5.1 (0.3) | 6.4* (0.2) | 6.4* (0 4) | 6.1* (0.3) | 6.4* (0.6) | 6.3* (0 5) | 6 6* (0.7) | at 1 h |
| Blood lactate (mmol litre$^{-1}$) | | | | | | | | | |
| Control | 0 84 (0.08) | 0.81 (0.08) | 0.63 (0.08) | 0.96 (0 14) | 0 72 (0.11) | 0.69 (0.08) | 0.67 (0 11) | 0 77 (0 11) | $P<0.05$ |
| Clonidine | 0.86 (0.06) | 0.65 (0.10) | 0.71 (0.06) | 0.72 (0 09) | 0.52*(0.05) | 0.77 (0 15) | 0 74 (0.11) | 0 76 (0.08) | at 4 h |
| Serum cortisol (nmol litre$^{-1}$) | | | | | | | | | |
| Control | 603 (65) | 581 (81) | 973* (88) | 1036* (57) | 1016* (101) | 935* (163) | 955 (95) | 683(113) | ns |
| Clonidine | 536 (69) | 501 (96) | 1120** (43) | 1183**(45) | 1146** (78) | 885* (134) | 814 (74) | 622 (94) | |
| Serum GH (miu litre$^{-1}$) | | | | | | | | | |
| Control | 2.1 | 11.2* | 6.0* | 11.6 | 4.5 | 1.8 | 6.1 | 4.7 | ns |
| | (0.3–17.7) | (0 3–85.9) | (0.5–131) | (0 3–35) | (0.5–20.1) | (0 3–5 2) | (1.9–23.7) | (2.1–23.5) | |
| Clonidine | 0.6 | 7.8* | 13.2** | 8.7 | 3 5 | 2.7 | 9 9 | 4.8 | |
| | (0.3–14.9) | (3.4–78.9) | (7.0–45.4) | (2.0–29.7) | (1.5–11.9) | (0.6–12.9) | (1.1–19.7) | (2.1–19.5) | |
| PCV(%) | | | | | | | | | |
| Control | 39 (0.7) | 35 (0.8) | 35 (0.9) | 34 (0.8) | 34 (1.0) | 34 (0.7) | 33 (0.8) | 33 (0.8) | ns |
| Clonidine | 40 (1.1) | 36 (1.3) | 35 (1.5) | 34 (1.4) | 34 (1.3) | 34 (1.8) | 32 (2 3) | 32 (1.4) | |

from a baseline value of 536 nmol litre$^{-1}$ at 1, 2, 4 ($P<0.01$) and 6 h ($P<0.05$) in the clonidine group. However, there were no significant differences between groups.

In both groups serum concentrations of GH increased transiently from baseline values at skin incision and at 1 h ($P<0.05$ in the control group, $P<0.05$ and $<0.01$ in the clonidine group). There were no significant differences between groups.

Blood glucose values increased significantly at 2 ($P<0.01$), 4, 6 and 12 h ($P<0.05$) in the control group and at all times, other than skin incision, in the clonidine group ($P<0.05$). At 1 h, blood glucose concentration was significantly greater in the clonidine group than in the control group ($P<0.05$).

Blood lactate concentrations did not change significantly throughout the study in the control group. In the clonidine group, blood lactate concentration was significantly lower than baseline at 4 h ($P<0.05$), and was also significantly lower at this time compared with the control group.

PCV decreased from baseline in both groups of patients, but this change was not statistically significant. There was no significant difference between groups.

## Discussion

We have shown that clonidine 3 $\mu$g kg$^{-1}$ i.v. decreased the cardiovascular, but not the pituitary hormonal, response to pelvic surgery.

The physiological response to surgical trauma includes an increase in circulating concentrations of the catabolic hormones, such as catecholamines, cortisol and GH, and a concomitant decrease in plasma concentrations of the anabolic hormones, such as insulin and testosterone.[14] Most anaesthetic techniques do not prevent these changes, but high doses of opioids and regional anaesthesia can modify the pituitary and sympathoadrenal response to surgery.

In this study, patients treated with clonidine had a decreased haemodynamic response to surgery, as shown by the lower values of heart rate, and systolic and diastolic arterial pressures, for 4 h after surgical incision. Thus the dose and method of administration of clonidine were adequate to test the hypothesis that clonidine could attenuate pituitary hormone secretion in addition to the cardiovascular response. However, we have clearly demonstrated no difference in GH and cortisol values after administration of clonidine.

Two previous studies have reported variable effects of clonidine on serum cortisol changes associated with surgery. In a study of 20 neurosurgical patients in which a significant decrease in serum cortisol concentration was reported, no samples were collected before oral administration of clonidine, and patients receiving high doses of steroids for less than 3 days were not excluded.[11] Pouttu and colleagues studied 21 patients undergoing breast surgery and found no difference in serum cortisol and GH concentrations when clonidine premedication was used. However, interpretation of the data is complicated by the use of diazepam premedication in the clonidine and control groups,[12] as benzodiazepines are known to alter ACTH and GH secretion.[15,16] In both of these studies, blood sampling was continued for a maximum of 3 h after surgery. As clonidine has a long half-life, neither study has assessed the effect of clonidine over an appropriate time period.

The hyperglycaemic response to surgery is multifactorial and results from increased secretion of catabolic hormones, particularly adrenaline and cortisol. Blood glucose concentrations increased significantly in both groups after surgery. Clonidine did not attenuate the hyperglycaemic response, despite the sympathoadrenal inhibition indicated by the haemodynamic changes. Paradoxically, blood glucose was significantly greater in the clonidine group 1 h after skin incision. A transient glycaemic effect of clonidine with an acute dose has been demonstrated, and clonidine is associated with direct inhibition of insulin secretion.[7,9] Our findings suggest that any hypoglycaemic effect of clonidine secondary to decreased sympathoadrenal activity is overcome by a direct inhibitory effect on the β-cells of the pancreas, and other catabolic hormones released in response to surgical stress.

We conclude that clonidine 3 $\mu$g kg$^{-1}$ i.v. at induction of anaesthesia failed to alter the pituitary–adrenal response to pelvic surgery.

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# Modelling the volume of expandable body fluid spaces during i.v. fluid therapy

L. STÅHLE, A. NILSSON AND R. G. HAHN

## Summary

We have developed mathematical models to represent the changes in volume of fluid spaces associated with i.v. administration of a crystalloid solution. Input data for parameter estimations were dilution of blood, measured as reduction of blood haemoglobin concentration. The models were based on the assumption that the body strives to maintain volume homeostasis of fluid spaces and that the rate of restoration is a function of deviation from resting volume. Two models were derived; the first had a single fluid space into which fluid was administered and from which fluid left, the other model had a second fluid space communicating with the first. These models may be useful in the description and analysis of the effects of i.v. fluid therapy. (*Br. J. Anaesth.* 1997; **78**: 138–143)

**Key words**
Fluids, i.v. Fluid balance. Pharmacokinetics. Model, mathematical.

The distribution of water between fluid compartments, such as the intracellular and extracellular spaces, has been studied in classical physiological work.[1] Tritiated water injected in trace amounts has also been used to describe the disposition of water in an organism.[2] In these studies, the water molecules have been assumed to be distributed within a fluid space of constant volume. Another, and quite different, aspect of water distribution is the changes in volume of fluid spaces when large, as opposed to trace, amounts of water are added to or removed from the body. In this situation, the infused water changes the volume of the fluid compartment it occupies. To our knowledge, this aspect of fluid therapy has not been studied previously. Therefore, we have developed mathematical models of changes in the volumes of the body fluid spaces applicable during and after volume loading.

## Methods

### THE MODELS

The models described here are referred to as volume-of-fluid-space (VOFS) models (fig. 1). To give the reader an image of the models, they may be thought of as water-filled balloons, because some features can be comprehended more easily by thinking of a fluid space as a volume surrounded by an elastic wall.

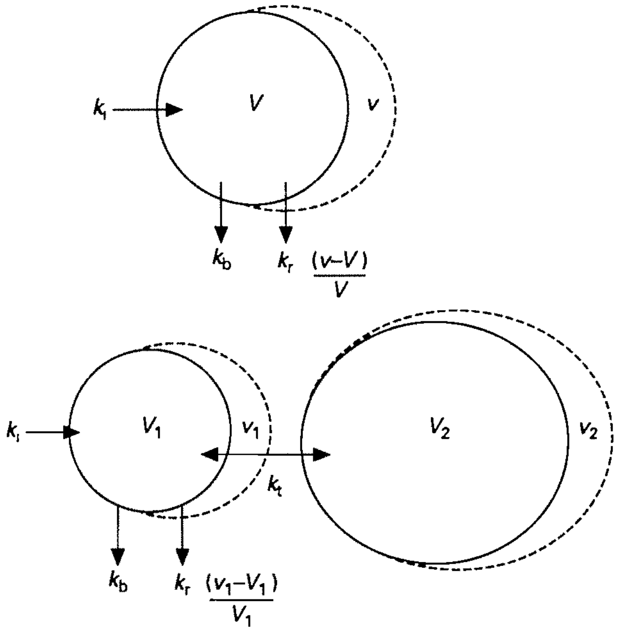

*Figure 1* Diagrammatic representations of the single-fluid space model, VOFS1 (upper) and the two-volume fluid space model, VOFS2 (lower). The broken lines indicate expansion of the fluid spaces.

The single-fluid space model, VOFS1, is based on the following assumptions: (1) during infusion, fluid enters an expandable fluid space of volume $v$, at a constant rate, $k_i$; (2) the expandable fluid space has a target volume $V$, which the body strives to maintain; (3) volume $v$ changes by fluid being eliminated from the fluid space at a basal rate, $k_b$ (perspiration and basal diuresis), and at a controlled rate. The controlled rate is proportional by a constant $k_r$ to the relative deviation of $v$ from the target volume $V$.

From these assumptions, the following differential equation can be derived:

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$$dv/dt = k_i - k_b - k_r\,(v - V)/V \qquad (1)$$

The solution to this equation is given in the appendix.

The two-fluid space model, VOFS2, is based on the following assumptions: (1) during infusion, fluid enters a primary expandable fluid space of volume $v_1$ at a constant rate, $k_i$; (2) there is a secondary expandable fluid space of volume, $v_2$, exchanging fluid with the primary fluid space; (3) $v_1$ changes through exchange with the secondary fluid space and as a result of fluid being eliminated from the primary fluid space at a basal rate, $k_b$, and at a controlled rate; (4) the primary and secondary fluid spaces have target volumes $V_1$ and $V_2$ which the system strives to maintain by acting upon the controlled elimination mechanism in proportion, $k_r$, to the relative deviation from the target volume of the primary fluid space and by acting upon the fluid exchange mechanism; (5) the net rate of fluid exchange between the fluid spaces is proportional to the difference in relative deviations from the target volumes by a constant $k_t$.

From these assumptions the following system of differential equations can be derived:

$$dv_1/dt = k_i - k_b - k_r\,(v_1 - V_1)/V_1 - k_t\,((v_1 - V_1)/V_1 - (v_2 - V_2)/V_2) \qquad (2)$$

$$dv_2/dt = k_t\,((v_1 - V_1)/V_1 - (v_2 - V_2)/V_2) \qquad (3)$$

The analytical solutions to these differential equations are presented in the appendix.

## NUMERICAL METHODS FOR ESTIMATING PARAMETERS

The rate constants $k_i$ and $k_b$ in equations (1–3) can be considered known; the first because it is under experimental control and the second because it (basal fluid loss) is a well established, but admittedly variable, physiological phenomenon. Also, the ratio $(v_1 - V_1)/V_1$ is known because it is the measured dilution of blood. This holds irrespective of whether $v_1$ corresponds only to blood volume or to blood volume and any fluid space which is in near instantaneous equilibrium with blood. The remaining variables $k_t$, $k_r$, $V_1$ and $V_2$ have to be estimated from the experimental data. This can be done by least-squares fitting of the solutions of equations (1–3) (see appendix) to experimental data.

We chose the random search method for the least-squares fitting procedure to obtain the best estimates of the unknown variables in the general form of the dilution–time curves in VOFS1 and VOFS2.[3] The variation in the parameters to be estimated was initially 0.1×rnd×pv, where rnd is a uniform random number between −1.0 and +1.0 and pv is the presently "best" value of the parameter. The process went on until no improvement of the fit was obtained in 15 trials and then the factor 0.1 was multiplied by 0.3×pv and the process repeated until no improvement was found within 0.001×pv. Calculations were performed on a Macintosh computer using Matlab version 3 (Math Works Inc., Notich, MA, USA). Experience from a large number of experiments analysed showed that convergence was rapid for data with a better fit to VOFS2 while poorly fitting data were accompanied by slow convergence.

## EXPERIMENTAL DATA

The curve-fitting procedure was illustrated by data obtained from two volunteer experiments where Ringer's acetate solution 25 ml $kg^{-1}$ was given by constant rate i.v. infusion over 30 min. The experiments were approved by the Ethics Committee at South Hospital, Stockholm.

Dilution occurring during i.v. infusion of crystalloid solutions can be assumed to indicate an increase in the volume of one or more expandable fluid spaces. Although many markers may be used to indicate dilution, we used blood haemoglobin (B-Hb) concentration, as measured by a Technicon H2 (Bayer, Tarrytown, NY, USA) using colorimetry at 546 nm. Plasma volume was taken to be (1−packed cell volume)×blood volume. Because our sampling perturbs the volume of the fluid space

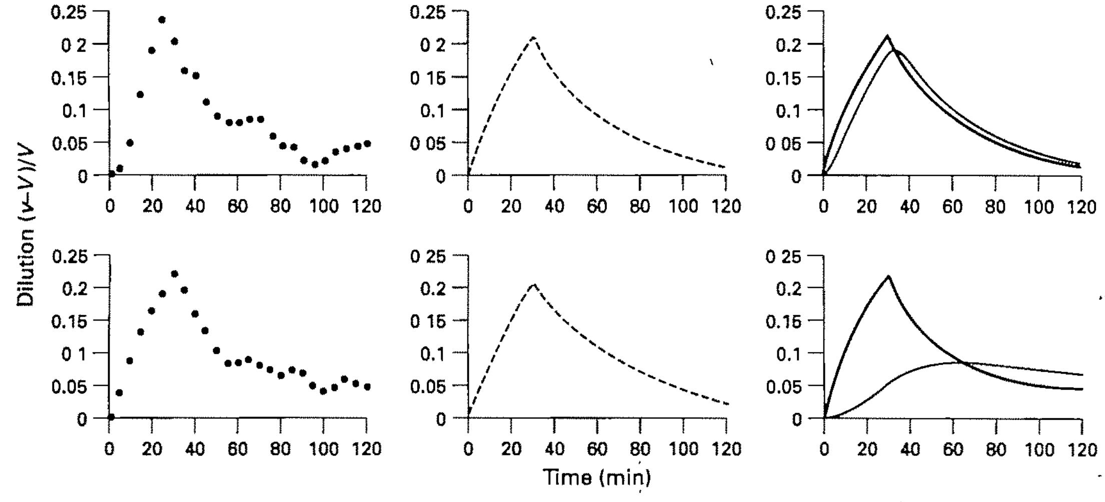

*Figure 2* Plasma dilution–time profiles in two volunteers in whom Ringer's solution 25 ml $kg^{-1}$ was given by i.v. infusion over 30 min (left) Curve-fitting of the same data was performed according to VOFS1 (middle) and VOFS2 (right), the latter showing the modelled dilution of both the primary (thick line) and secondary (thin line) fluid space. A statistical test applied on the residual errors showed that VOFS1 was most suitable for presentation in first volunteer (top row) while VOFS2 was more appropriate in the second volunteer (bottom row).

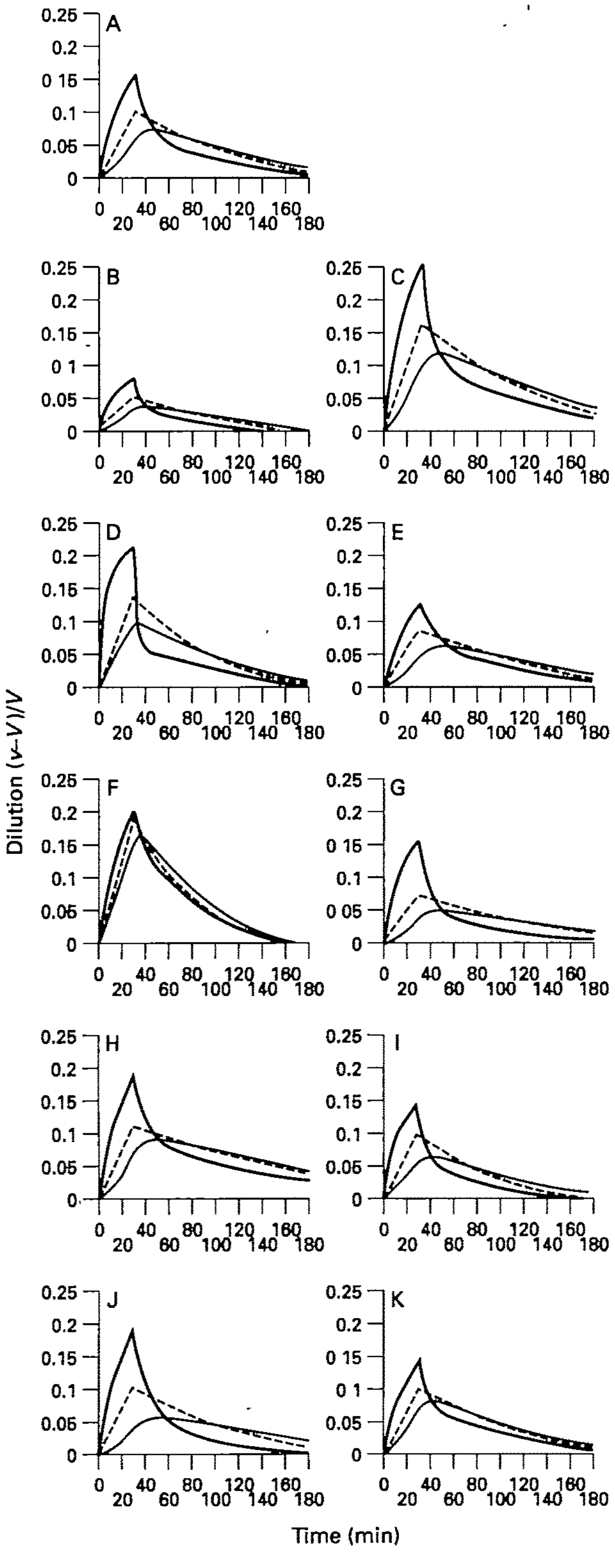

*Figure 3* Simulation of the dilution–time profiles of the primary (thick line) and secondary (thin line) fluid spaces in the VOFS2 with parameters set as shown in table 2. The corresponding curve (broken line) for the VOFS1 model is also shown.

measured, a correction was introduced based on multiplying the sample volume by the sample B-Hb concentration and then subtracting the amount obtained from total body Hb content, as calculated from estimated blood volume.[4] There are several equations available for estimation of total blood volume from the length and height of human subjects; all give similar results. In this study, the equation of Nadler, Hidalgo and Bloch[5] was used. The dilution–time curves were analysed according to both the VOFS1 and VOFS2 models and a statistical test was applied to the residual errors to select the best for presentation.[3]

### MODEL SENSITIVITY TO NOISE

Identifiableness of parameters was investigated by simulating "exact" data and then estimating them by least squares. Feeding exact data to the program resulted in an output within the precision preset for the algorithm (less than 0.001).

Simulation of statistical error was also performed. For each parameter combination shown in table 2, $(v_1 - V_1)/V_1$ was calculated for various times. A random, normally distributed error was then added to each value to investigate the sensitivity of the parameter estimations to noise. The size of the error, and the use of an additive error model, were based on the real situation. B-Hb is a method with an SD of approximately 1 unit of measurement, which is less than 1%. When used to estimate dilution of plasma, the difference between two Hb values is used and the relative size of the error becomes larger than the assay precision. However, the relative size of the error also depends on the magnitude of the dilution. We therefore chose to allow the error to be independent of the parameters and dilution in order to mimic the real situation. Thus, the "standard" SD was chosen as 0.010 dilution units corresponding to approximately 1.4 g litre$^{-1}$ Hb units. Inspection of the simulation curves shows that they are slightly worse, in terms of error, than real data. The number of times were 12 (0, 2, 6, 12, 20, 22, 26, 32, 40, 50, 90 and 120 min after the start of infusion). For every parameter combination, 25 data sets were simulated, each with random errors, and fitted. Mean, SD, median and, in some cases, geometric mean were calculated.

## Results

The VOFS1 model was most suitable for presentation in the first volunteer experiment (fig. 2, upper row). In this case, dilution was similar in the primary

*Table 1* Results of volume kinetic analysis of the infusion experiments shown in figure 2. Two adult male volunteers were given Ringer's solution i.v. *VOFS2 is most appropriate when the test value <3.47.

| | Volunteer | |
|---|---|---|
| | 1 | 2 |
| Age (yr) | 30 | 31 |
| Length (cm) | 186 | 190 |
| Body weight (kg) | 85 | 95 |
| VOFS1 model | | |
| $V$ (litre) | 6.4 | 7.1 |
| $k_r$ (ml min$^{-1}$) | 177 | 148 |
| VOFS2 model | | |
| $V_1$ (litre) | 4.9 | 5.4 |
| $V_2$ (litre) | 1.6 | 9.1 |
| $k_r$ (ml min$^{-1}$) | 171 | 83 |
| $k_t$ (ml min$^{-1}$) | 320 | 147 |
| $F$ test * | 0.01 | 23.8 |

*Table 2* Simulated parameter values used to generate the curves in figure 3 (A–K). For all curves $k_b$=2.5 ml min$^{-1}$ and the infusion time is 30 min

| Figure 3 | $V_1$ (litre) | $V_2$ (litre) | $k_r$ | $k_t$ (ml min$^{-1}$) | $k_i$ |
|---|---|---|---|---|---|
| A | 4 | 8 | 100 | 200 | 50 |
| B | 4 | 8 | 100 | 200 | 25 |
| C | 4 | 8 | 100 | 200 | 75 |
| D | 1 | 8 | 100 | 200 | 50 |
| E | 7 | 8 | 100 | 200 | 50 |
| F | 4 | 2 | 100 | 200 | 50 |
| G | 4 | 14 | 100 | 200 | 50 |
| H | 4 | 8 | 50 | 200 | 50 |
| I | 4 | 8 | 150 | 200 | 50 |
| J | 4 | 8 | 100 | 100 | 50 |
| K | 4 | 8 | 100 | 300 | 50 |

and secondary fluid spaces, which is expected when the VOFS2 model is not significantly "better" than the VOFS1 model. This indicates that the infused fluid diluted a single fluid space. In contrast, VOFS2 was more appropriate in the second volunteer experiment. Here the dilution was different in the primary and secondary fluid spaces (fig. 2, lower row). Data generated in the volume kinetic analyses are shown in table 1.

The reproducibility of the parameter estimates using different seeds for the random number generator was within 1%.

In the simulation of statistical error, the parameters were varied, as shown in table 2 and illustrated

*Table 3* Statistical simulation of the influence of parameter values, experimental conditions and statistical error on the precision and bias of the parameter estimates. $k_b$ was set to 2.5 ml min$^{-1}$. The infusion time was 30 min and 25 simulations were used to obtain the statistics for each parameter combination. SD=standard deviation around the simulated dilution curve, expressed in dilution units

| Parameter combination and statistics | $V_1$ (litre) | $V_2$ (litre) | $k_r$ | $k_t$ (ml min$^{-1}$) | $k_i$ | SD |
|---|---|---|---|---|---|---|
| A | 4 | 8 | 100 | 200 | 50 | 0.005 |
| Mean | 4.00 | 9.32 | 94 | 210 | | |
| SD | 0.23 | 3.45 | 28 | 34 | | |
| Median/geom. mean | 4.06 | 8.93/8.68 | 92 | 206 | | |
| | 4 | 8 | 100 | 200 | 50 | 0.01 |
| Mean | 3.87 | 9.61 | 101 | 240 | | |
| SD | 0.58 | 7.25 | 39 | 71 | | |
| Median/geom. mean | 3.92 | 7.41/7.71 | 103 | 243 | | |
| | 4 | 8 | 100 | 200 | 50 | 0.015 |
| Mean | 4.13 | 12.67 | 84 | 235 | | |
| SD | 0.88 | 8.43 | 53 | 96 | | |
| Median/geom. mean | 4.11 | 13.03/9.62 | 66 | 227 | | |
| B | 4 | 8 | 100 | 200 | 25 | 0.01 |
| Mean | 3.96 | 13.87 | 95 | 245 | | |
| SD | 1.21 | 7.64 | 62 | 210 | | |
| Median/geom. mean | 3.81 | 12.89/11.5 | 97 | 205 | | |
| C | 4 | 8 | 100 | 200 | 75 | 0 01 |
| Mean | 3.93 | 8.76 | 100 | 211 | | |
| SD | 0.36 | 3.49 | 29 | 41 | | |
| Median/geom. mean | 3.93 | 8.47/8.12 | 102 | 211 | | |
| D | 1 | 8 | 100 | 200 | 50 | 0.01 |
| Mean | 0.99 | 8.70 | 94 | 209 | | |
| SD | 0.13 | 3.01 | 31 | 36 | | |
| Median | 1.00 | 9.31 | 97 | 203 | | |
| E | 7 | 8 | 100 | 200 | 50 | 0.01 |
| Mean | 6.78 | 9.58 | 100 | 260 | | |
| SD | 1.30 | 4.29 | 38 | 246 | | |
| Median | 6.97 | 8.99 | 112 | 207 | | |
| F | 4 | 2 | 100 | 200 | 50 | 0.01 |
| Mean | 3.79 | 2.43 | 100 | 339 | | |
| SD | 0.86 | 1.09 | 18 | 275 | | |
| Median | 3.92 | 2.64 | 99 | 233 | | |
| G | 4 | 14 | 100 | 200 | 50 | 0.01 |
| Mean | 4.16 | 16.16 | 113 | 194 | | |
| SD | 0.61 | 7.72 | 38 | 54 | | |
| Median | 4.10 | 17.11 | 110 | 187 | | |
| H | 4 | 8 | 50 | 200 | 50 | 0.01 |
| Mean | 3.86 | 7.34 | 56 | 233 | | |
| SD | 0.69 | 3.23 | 27 | 71 | | |
| Median | 3.63 | 6.81 | 53 | 225 | | |
| I | 4 | 8 | 150 | 200 | 50 | 0.01 |
| Mean | 4.01 | 12.46 | 133 | 226 | | |
| SD | 0.67 | 7.39 | 71 | 104 | | |
| Median | 4.03 | 11.60 | 134 | 263 | | |
| J | 4 | 8 | 100 | 100 | 50 | 0.01 |
| Mean | 3.92 | 7.62 | 99 | 110 | | |
| h | 0.35 | 3.06 | 21 | 29 | | |
| Median | 4.00 | 8.08 | 103 | 111 | | |
| K | 4 | 8 | 100 | 300 | 50 | 0 01 |
| Mean | 3.69 | 9.89 | 96 | 379 | | |
| SD | 0.92 | 4.39 | 31 | 174 | | |
| Median | 3.69 | 8.39 | 101 | 337 | | |

further in figure 3. The results revealed acceptable precision and lack of bias for $V_1$ and $k_r$ (table 3). In contrast, $V_2$ and $k_t$ were more sensitive to statistical error and their distributions were also skewed. There was a negative correlation between estimates of $V_1$ and $k_t$, which illustrates that VOFS is a non-linear model.

## Discussion

The clinical basis for this study was the need for methods that allow estimation of the volumes and kinetics of fluid spaces in the body influenced by i.v. infusion of large amounts of fluids. Such methods may be useful for designing and optimizing i.v. fluid therapy. In fact, little is known of how fluid should be administered to yield a certain volume response. Clinical practice is currently the basis for most schemes used.

There are several fundamental differences between the VOFS and traditional pharmacokinetic models. The latter describe the distribution of a solute into fluid spaces and binding sites, which themselves are assumed not to be affected by the solute. The volume of distribution is considered to be a constant. Similarly, the target volume of a VOFS model is assumed to be constant, but the size of the fluid space expanded is changed. The size of a target volume can be found only by expanding the fluid space because it is the expandability that distinguishes this fluid space from other parts of the body water.

One important feature of our models is that they take into account differences in compliance with regard to volume expansion between tissues. For example, oedema is usually apparent in the lungs and in the subcutaneous tissue of the legs and around the eyes, while the brain and skeleton are almost unaffected. This illustrates that expandable fluid spaces in a patient are not synonymous with the body fluid compartments usually related to in physiological textbooks. Although the water molecules in a crystalloid solution are distributed throughout the extracellular fluid space, the same fluid might expand a much smaller volume.

A concept of two functionally distinct, but communicating, fluid spaces, one which is rigid and the other expandable, is shown in figure 4. The difference between the distribution of a trace amount of water injected, the molecules of which may reach any part of the two connected fluid spaces, and the change in volume resulting from an infusion is crucial for the understanding of the VOFS models. A component necessary for estimation of the size of the expandable volume is the existence of the measurable substance confined exclusively to the sampled space. Blood haemoglobin fulfils this criterion.

To avoid confusion, the terminology for the VOFS models was chosen to differ from that used in classical pharmacokinetics. For example, the volume of distribution and clearance of the infused water molecules vary during i.v. infusion. The target volume is a more suitable term as it remains constant. Apart from the differences in terms of interpretation, the mathematical solutions and data analysis have much in common with those used for compartmental models in traditional pharmacokinetics. The VOFS models are based on the assumption that plasma dilution follows a curve with a monoexponential or biexponential component. Non-linear least-squares regression fitting is performed on patient data to obtain estimates of the unknown parameters in these equations. Thereafter, the analytical solutions to the differential equations based on the VOFS model assumptions are used to calculate the sizes of the expandable fluid spaces and the kinetic constants determining the distribution of fluid.

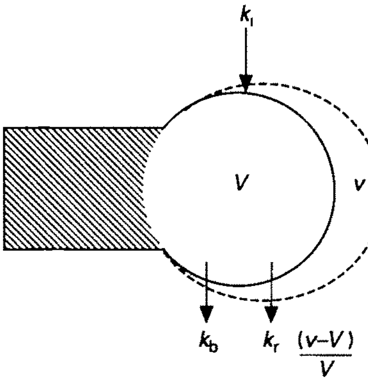

*Figure 4* Illustration of the difference in principle between trace amount pharmacokinetics and volume kinetics. A water molecule entering the fluid space consisting of one expandable portion and one rigid portion can be found anywhere and therefore has a volume of distribution, being the sum of the two portions of the entire fluid space. In terms of volume, however, only the expandable portion of the fluid space is influenced by added water molecules.

The results of the simulations of different parameter values demonstrate that dilution of blood varies considerably depending on the sizes of the fluid spaces and the rapidity of the transport between them. It is of interest that our calculations gave the dilution–time profile of a secondary fluid space, which probably corresponds to the extracellular fluid of some peripheral tissues. This has previously been difficult to study. The fact that a secondary fluid space may be detected has implications for the design of optimal i.v. fluid therapy and, possibly, to the choice of strategy in oedema treatment.

The statistical simulations showed some important properties of our model. The non-linearity of the parameters was reflected in a correlation between parameter estimates. This non-linearity also expressed itself in the distributions of $V_2$ and $k_t$, which tended to be positively skewed in some circumstances which can, to some extent, be controlled for in clinical and experimental work. In particular, the dilution measurement needs to be precise because, if the dilution is small owing to a small $k_i$, the error may be very large in comparison with the dilution and result in overestimation of $V_2$ and $k_t$. One method of improving the estimate of the parameters is to use the geometric mean, unless the experimental conditions can be improved by increasing the dose of the fluid given, shortening the infusion time or using a more precise haemoglobin assay.

Approximately 100 i.v. infusions have been carried out for which volume kinetics have been calculated. Our experience with these models is that they "behave well" when real data are applied. Biological findings obtained using the VOFS models, and recommendations for infusion rates, are discussed in subsequent studies.

## Appendix

### SOLUTION OF VOFS1

Equation (1) is readily solved by standard methods[6] giving:

$$\frac{v-V}{V}=\frac{k_i-k_b}{k_r}+\frac{Qe^{-k_r t/V}}{V} \tag{4}$$

Here $Q$=unknown constant which must be determined by initial conditions. At the start of the infusion when $t=0$ it is assumed that $v=V$, giving the solution:

$$\frac{v-V}{V}=\frac{(k_i-k_b)\ (1-e^{-k_r t/V})}{k_r} \tag{5}$$

After infusion, the solution becomes:

$$\frac{v-V}{V}=(W_T+\frac{k_b}{k_r})e^{-k_r(t-T)/V}-\frac{k_b}{k_r} \tag{6}$$

where $w_T=(v(T)-V)/V$, that is the relative volume deviation attained after $T$ minutes of infusion.

### SOLUTION OF VOFS2

The system (equations (2, 3)) has the form of a non-homogeneous system of linear first-order differential equations. A particular solution, the steady state solution $v_{1_p}$=A, $v_{2_p}$=B, is found by setting $dv_1/dt=dv_2/dt=0$, the solution of which is:

$$v_{1_p}=A=\frac{(k_i-k_b+k_r)V_1}{k_r} \tag{7}$$

$$v_{2_p}=B=\frac{(k_i-k_b+k_r)V_2}{k_r} \tag{8}$$

This particular solution is (below) added to the solution of the corresponding homogeneous system of equations to obtain the general solution $v_1$, $v_2$ to the system (equations (2, 3)). After some preliminary calculations, one obtains:

$$v_1=Ee^{Xt}+Fe^{Yt}+A \tag{9}$$

$$v_2=Ge^{Xt}+He^{Yt}+B \tag{10}$$

where

$$X=1/2[-(\frac{(k_r+k_t)}{V_1}+\frac{k_t}{V_2})+\sqrt{(\frac{(k_r+k_t)}{V_1}-\frac{k_t}{V_2})^2+\frac{4k_t^2}{V_1V_2}}] \tag{11}$$

$$Y=1/2[-(\frac{(k_r+k_t)}{V_1}+\frac{k_t}{V_2})-\sqrt{(\frac{(k_r+k_t)}{V_1}-\frac{k_t}{V_2})^2+\frac{4k_t^2}{V_1V_2}}] \tag{12}$$

Note that both $X$ and $Y$ are negative numbers. In order to find G and H, the determinantal equations associated with $X$ and $Y$ can be used to obtain:

$$G=\frac{Ek_t}{V_1X+k_tV_1/V_2} \tag{13}$$

$$H=\frac{Fk_t}{V_1Y+k_tV_1/V_2} \tag{14}$$

The general solution to the system (equations (2, 3)) is therefore:

$$v_1=Ee^{Xt}+Fe^{Yt}+\frac{(k_i-k_b+k_r)V_1}{k_r} \tag{15}$$

$$v_2=\frac{k_tEe^{Xt}}{V_1X+k_tV_1/V_2}+\frac{k_tFe^{Yt}}{V_1Y+k_tV_1/V_2}+\frac{(k_i-k_b+k_r)V_2}{k_r} \tag{16}$$

with $X$ and $Y$ as in equation (11) and equation (12), and E and F are determined by the initial conditions. As in the case of VOFS1 there are two different initial conditions. At the start of the experiment, steady state is assumed and thus $v_1=V_1$ and $v_2=V_2$ at time $t=0$. Thence:

$$V_1=E+F+A \tag{17}$$

$$V_2=\frac{Ek_t}{V_1X+k_tV_1/V_2}+\frac{Fk_t}{V_1Y+k_tV_1/V_2}+B \tag{18}$$

Rewriting to conform with the experimental data, $X$, $Y$, $Q_1$, $Q_2$ and $Q_3$ can be estimated from the dilution data from the following expression, which is valid *during infusion*:

$$w_1=\frac{v_1-V_1}{V_1}=\frac{Ee^{Xt}+Fe^{Yt}+A-V_1}{V_1}=Q_1e^{Xt}+Q_2e^{Yt}+Q_3 \tag{19}$$

where, after some calculations, $Q_1$, $Q_2$, and $Q_3$ are obtained from:

$$Q_1=-Q_2-Q_3 \tag{20}$$

$$Q_2=(k_i-k_b)\frac{1-Z}{k_r(Z-U)} \tag{21}$$

$$Q_3=\frac{(k_i-k_b)}{k_r} \tag{22}$$

where

$$Z=\frac{k_t}{V_2X+k_t} \tag{23}$$

$$U=\frac{k_t}{V_2Y+k_t} \tag{24}$$

The conditions for the solution *after infusion* are $w_{1T}=(v_1(T)-V_1)/V_1$ at $T$ minutes of infusion and correspondingly $w_{2T}=(v_2(T)-V_2)/V_2$. The exponents $X$ and $Y$ are not changed. Prime notation is used to distinguish the parameters valid after infusion from parameters during infusion. For simplification, the time variable $t$ is reset to zero and the solution can be written:

$$\frac{v_1-V_1}{V_1}=Q1'e^{Xt}+Q2'e^{Yt}+Q3' \tag{25}$$

where

$$Q1'=w_{1T}-\frac{Z(w_{1T}+k_b/k_r)-k_b/k_r-w_{2T}}{Z-U}+\frac{k_b}{k_r} \tag{26}$$

$$Q2'=\frac{Z(w_{1T}+k_b/k_r)-k_b/k_r-w_{2T}}{Z-U} \tag{27}$$

$$Q3'=-k_b/k_r \tag{28}$$

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# Volume kinetics of Ringer's solution in female volunteers

R. G. HAHN, D. DROBIN AND L. STÅHLE

**Summary**

The kinetics of crystalloid solutions in humans have not been adequately described previously. Therefore, we measured blood haemoglobin concentration during and for 120 min after i.v. infusion of 25 ml $kg^{-1}$ of Ringer's acetate solution over 15, 30, 45 and 80 min, and 12.5 ml $kg^{-1}$ over 30 min in six adult female volunteers. The dilution–time profiles were analysed according to a new kinetic model adapted for fluid spaces. Volume expansion produced by Ringer's solution approached steady state in an exponentially decaying manner when plasma volume had increased by approximately 550 ml. The size of the fluid space expanded by Ringer's solution was only 4.8 litre (95% confidence interval 3.8–5.8 litre) except for the fastest infusion, where it averaged 9.0 litre. The rate of fluid elimination could be predicted as the product of plasma dilution and a constant averaging 95 (95% confidence interval 68–122) ml $min^{-1}$. (*Br. J. Anaesth.* 1997; **78**: 144–148)

**Key words**

Blood, volume. Fluids, i.v. Pharmacokinetics. Model, mathematical.

Expansion of the intravascular volume is an important property of crystalloid solutions given by i.v. infusion. The currently available methods used to describe this effect consist primarily of repeated measurement of blood volume by a radioactive isotope or dye.[1 2] For accurate results, these methods require an unchanged blood volume for 30–40 min during equilibration of the tracer, which makes them poorly suited for studies of non-steady-state conditions during fluid loading, hypotension and surgery. Changes in blood volume may also be indicated by haemodilution[3 4] but this approach has not been adopted widely.

The aim of this study was to describe the disposition of Ringer's solution in the body when infused at different rates using a new kinetic model.[5] We used dilution–time curves to estimate the size of the expandable space(s) into which the fluid is distributed. Pharmacokinetic principles adapted for fluid volumes were used to model the dynamic conditions during volume loading.

## Subjects and methods

Ringer's acetate solution was given on a total of 30 occasions to six healthy female volunteers, aged 23–46 yr (mean 32 yr) and with a body weight of 50–75 kg (mean 60 kg). The study was approved by the local Ethics Committee and each volunteer gave informed consent.

Volunteers ate a light meal (consisting of one cup of coffee, tea or water and one sandwich) at home before going to hospital where the experiments were started at 08:00–10:00. No oral fluid or food was allowed between the morning meal and the end of the study. Volunteers voided, were immediately placed comfortably on a bed, and 20 min of equilibration was allowed before the infusions were started.

Cannulae were placed into the antecubital veins of both arms and Ringer's acetate solution (Pharmacia, Uppsala, Sweden; electrolyte content (mmol $litre^{-1}$): Na 130, K 4, Ca 2, Mg 1, acetate 30 and Cl 110) was infused into one of these veins at a constant rate with the aid of one or several infusion pumps (IVAC 560, San Diego, CA, USA). Volunteers received, in random order and at intervals of at least 1 day, an i.v. infusion of Ringer's acetate 25 ml $kg^{-1}$ over 15, 30, 45 and 80 min, and 12.5 ml $kg^{-1}$ over 30 min.

### MEASUREMENTS

Samples (3 ml) for measurement of blood haemoglobin (B-Hb) concentration using a Coulter Counter STKS (Counter Electronics, Hialeah, FL, USA) were obtained from the venous cannula not used for infusion before the infusion, every 10 min during infusion, and at 0, 5, 10, 15, 20, 25, 30, 60, 80, 100 and 120 min after infusion. After a blood sample was obtained, Ringer's solution 2 ml was injected to flush the cannula and a small discard sample was obtained before each blood sample to avoid undue haemodilution caused by this fluid. The first B-Hb sample in the series was obtained in duplicate and the mean was used in calculations.

In 25 experiments, urine volume was measured after blood had been collected at 30 and 120 min after the infusion had ended.

### CALCULATIONS

Blood volume (BV) before treatment ($BV_0$) was calculated according to Nadler, Hidalgo and Bloch.[6]

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BV during treatment ($BV_n$) was estimated from dilution of B-Hb. The fraction of the infused Ringer's acetate solution that remained in blood (%) was calculated, without correction for blood sampling, from the quotient of BV change by the infused volume[4]:

$BV_0$ (litre)=

$$0.03308\ \text{weight (kg)}+0.3561\ \text{length}^3\ \text{(m)}+0.1833$$

$$BV_n=BV_0\times \text{B-Hb}_0\ /\ \text{B-Hb}_n$$

Fluid retained (%)=

$$100\ (BV_n-BV_0)/\text{volume infused}$$

The kinetics of fluid loading were analysed with the aid of the volume-of-fluid-space (VOFS) models, which are based on the assumption that the volume of the fluid space into which the fluid is distributed strives to be maintained in a way similar to one or two elastic balloons. The assumptions on which these kinetic models are based are summarized in figure 1. The equations used for the calculations have been given previously.[5]

Dilution of B-Hb concentration, with a correction made for loss of haemoglobin and fluid resulting from blood sampling, was used to indicate the water load in the VOFS models. As Ringer's solution essentially remains outside the erythrocytes, calculations were based on plasma volume, which was taken to be the product of (1−packed cell volume) and estimated blood volume. During the experiment, packed cell volume was assumed to decrease in proportion to dilution of B-Hb, which is not unrealistic as the infused fluid is isotonic.

The one-fluid space model (VOFS1) uses non-linear least-squares regression to calculate the baseline (target) volume of the expanded fluid space expanded by the infusion ($V$) and the elimination rate constant ($k_r$) and to predict fluid loss (sum of urine excretion and perspiration) during the experiment. Basal fluid loss ($k_b$) was set at 1.0 ml $\text{min}^{-1}$. The two-fluid space model (VOFS2) gives the target volumes of the central and peripheral fluid spaces expanded by the infusion ($V_1$ and $V_2$), rate constant for the diffusion of fluid between these fluid spaces ($k_t$), elimination rate constant ($k_r$) and fluid loss. A partial $F$ test was applied to the residual errors (sum of squares) to select the best model for presentation.[7]

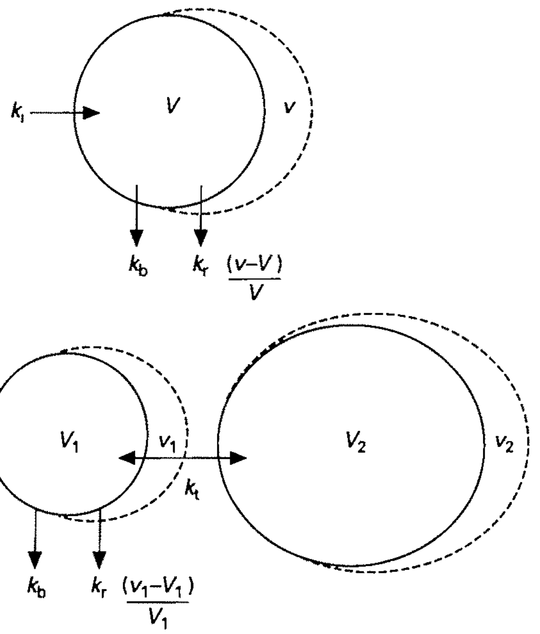

*Figure 1* Schematic diagram of the VOFS1 (upper) and VOFS2 (lower) models. Fluid is infused at a constant rate ($k_i$) and enters a space having the volume ($v$) which changes as a result of fluid leaving the space at a basal rate ($k_b$) and at a controlled rate ($k_r$) proportional to the deviation from the target value ($V$). In VOFS2, a secondary fluid space of volume ($v_2$) which exchanges fluid with the primary fluid space ($v_1$) and the rate of volume equlibration between them is proportional to the difference in the relative deviation from the target value by a constant ($k_t$).

The results are expressed as mean (95% confidence interval). The standard error of the mean (SEM) was used when the data were based on only six experiments. The statistical evaluation also comprised one-way and two-way analyses of variance (ANOVA), repeated-measures ANOVA followed by the Scheffé test, and simple linear regression analysis. $P<0.05$ was considered significant.

## Results

The highest infusion rate (25 ml $\text{kg}^{-1}$ over 15 min) was associated with mild symptoms in all volunteers. Subjects reported a sense of swelling in the hands or face ($n=3$), an abdominal lump ($n=2$), slight dyspnoea ($n=3$), headache ($n=1$) and analgesia around the lips ($n=1$). Occasional complaints of "feeling swollen" were noted during a few other experiments, but these symptoms were very mild.

The fraction of fluid given that remained in blood was higher than the expected 20% during all infusions and for the first 30 min thereafter. Ringer's solution was a more effective plasma expander when it was infused slowly (fig. 2). Blood volume increased by a maximum of 550 ml regardless of how fast the solution was infused (fig. 3).

The dilution–time curves were then analysed according to the one- and two-fluid space models, VOFS1 and VOFS2 (figs 1, 3). Only 10 of the 30 dilution–time curves were more adequately described by VOFS2 (table 1).

When using the most appropriate model for each experiment, two-way ANOVA showed that the size

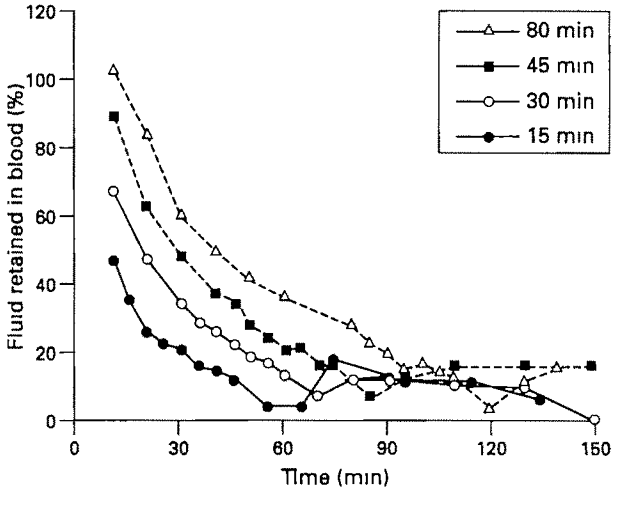

*Figure 2* Fraction of the infused fluid (mean) indicated by haemodilution to be retained in blood during and after infusion of Ringer's acetate solution 25 ml $\text{kg}^{-1}$ in six female volunteers. Time 0=start of infusion.

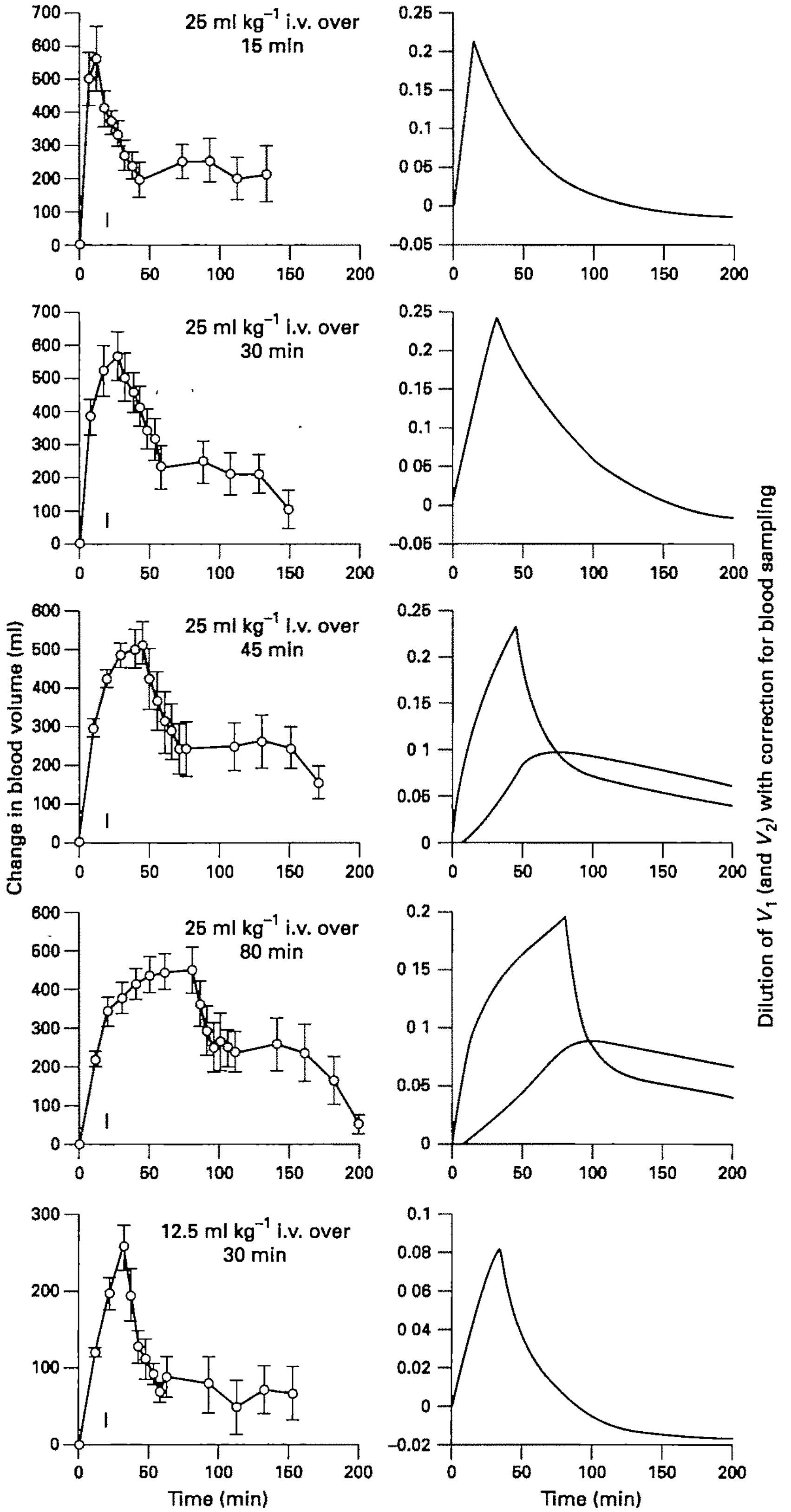

*Figure 3* Change in blood volume (mean, SEM) indicated by haemodilution when Ringer's acetate solution is infused in six female volunteers (left column). The same data with correction for blood sampling analysed by the volume-of-fluid-space models and presented as dilution of the central and (when applicable) peripheral fluid spaces expanded by the infusion (I) (right column).

of the expanded body fluid space ($V$ or $V_1+V_2$) was associated both with the infusion regimen ($P<0.01$) and the subject ($P<0.02$; interaction effect $P<0.04$). These significance levels became stronger when $V$ or $V_1+V_2$ was divided by body weight.

When mean values for each infusion rate were compared, however, it appeared that 12.5 ml kg$^{-1}$ expanded a fluid space of similar size to that expanded by 25 ml kg$^{-1}$ when infused at the low and intermediate rates (mean 4.8 litre (95% confidence

*Table 1* Volume kinetic analysis and urine excretion in experiments with i.v. infusions of Ringer's acetate solution in six female volunteers (mean (SEM)). *Paired difference between predicted fluid loss and measured urine volume

| Infusion time | Dose 25 ml $kg^{-1}$<br>15 min | 30 min | 45 min | 80 min | Dose 12.5 ml $kg^{-1}$<br>30 min |
|---|---|---|---|---|---|
| One-fluid space (*n*) | 4 | 6 | 2 | 3 | 5 |
| Two-fluid spaces (*n*) | 2 | 0 | 4 | 3 | 1 |
| $V$ or $V_1+V_2$ (litre) | 9.0 (1.2) | 4.8 (0.5) | 4.4 (0.9) | 4.5 (1.2) | 5.5 (1.3) |
| $k_r$ (ml $min^{-1}$) | 79 (33) | 105 (11) | 102 (43) | 67 (23) | 140 (41) |
| Measured urine (*n*) | 6 | 5 | 6 | 4 | 4 |
| Measured urine (litre) | 0.99 (0.08) | 1.06 (0.15) | 0.93 (0.18) | 0.92 (0.20) | 0.64 (0.12) |
| Bias urine (litre)* | −0.13 (0.13) | 0.26 (0.17) | 0.00 (0.09) | 0.26 (0.08) | 0.18 (0.09) |

*Table 2* Volume kinetic data and measured urine volume in experiments where the one-fluid space model or the two-fluid space model, respectively, was optimal (mean (95% confidence interval). *As predicted by the VOFS model in experiments where urine was collected

|  | One-fluid space | Two-fluid spaces | *P* ANOVA |
|---|---|---|---|
| Experiments (*n*) | 20 | 10 |  |
| $V$ or $V_1+V_2$ (litre) | 4.6 (3.6–5.6) | 7.7 (5.2–10.2) | <0.005 |
| $k_r$ (ml $min^{-1}$) | 125 (93–156) | 36 (11–62) | <0.001 |
| $k_t$ (ml $min^{-1}$) | — | 148 (88-208) |  |
| Urine collected (*n*) | 16 | 9 |  |
| Urine 30 min (litre) | 0.73 (0.58–0.89) | 0.50 (0.31–0.68) | <0.044 |
| Urine/fluid load (%) | 52 (18–71) | 33 (10–53) | <0.001 |
| Measured urine 2 h (litre) | 1.05 (0.87–1.22) | 0.70 (0.52–0.87) | <0.011 |
| Urine/fluid load (%) | 75 (0.47–1.08) | 48 (32–66) | <0.001 |
| Fluid loss (litre)* | 1.26 (1.04–1.49) | 0.56 (0.34–0.78) | <0.001 |

*Table 3* Subject characteristics, volume kinetic data and measured urinary excretion after infusion for the female volunteers who participated in experiments with i.v. infusions of Ringer's solution (mean (SEM))

| Subject No | Age (yr) | Body weight (kg) | $V$ or $V_1+V_2$ (litre) | $k_r$ (ml $min^{-1}$) | One-fluid space (*n*) | Urine excreted (ml)<br>30 min | 120 min |
|---|---|---|---|---|---|---|---|
| 1 | 46 | 70 | 3.9 (0.7) | 210 (22) | 5 | 978 (127) | 1355 (133) |
| 2 | 40 | 75 | 6.6 (1.5) | 96 (30) | 3 | 583 (112) | 848 (75) |
| 3 | 31 | 50 | 3.8 (1.1) | 77 (14) | 4 | 675 (81) | 926 (137) |
| 4 | 27 | 60 | 5.6 (1.9) | 72 (17) | 3 | 742 (112) | 941 (122) |
| 5 | 27 | 58 | 5.5 (0.5) | 62 (33) | 3 | 417 (122) | 716 (137) |
| 6 | 30 | 55 | 8.4 (1.0) | 54 (16) | 2 | 406 (120) | 580 (114) |

interval 3.8–5.8 litre)) while it was almost twice as large when 25 ml $kg^{-1}$ was given over 15 min ($P<0.05$ by repeated-measures ANOVA) (table 1).

In the 10 experiments in which VOFS2 was optimal, $V_1$ was 2.6 (1.9–3.4) litre and $V_2$ amounted to 6.4 (3.8–9.1) litre. The total expandable volume was significantly larger compared with experiments in which the one-fluid space model was sufficient (table 2).The value of the elimination rate constant $k_r$ differed significantly between subjects (ANOVA $P<0.01$) but not between infusion rates (table 3). For the entire series of experiments, the mean value of $k_r$ was 95 (68–122) ml $min^{-1}$.

Data on urine volume were consistent with results of volume kinetic analysis. Hence, the measured urine volume correlated with the calculated $k_r$ (fig. 4). In the experiments where VOFS2 was optimal, not only $k_r$ and predicted fluid loss, but also urine volume were low (table 2). Some volunteers, notably those who often handled the fluid load according to VOFS1, voided more promptly than others (table 3).

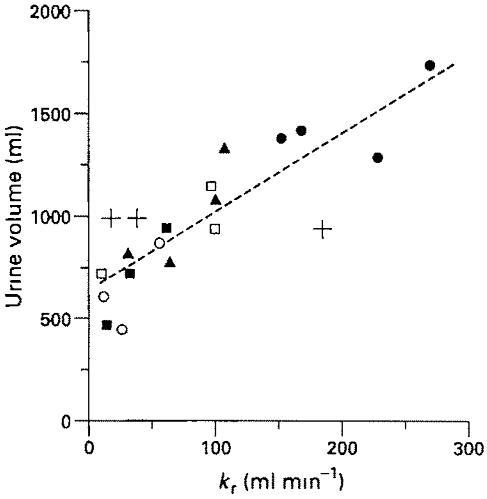

*Figure 4* Relationship between rate constant for dilution-dependent elimination ($k_r$) in the most accurate volume-of-fluid-space model *vs* total urine output when 25 ml $kg^{-1}$ of Ringer's acetate was given by i.v infusion A different symbol is used for each of the six volunteers. $r=0.83$, $P<0.001$

## Discussion

The initial data analysis showed results that differ from the accepted view of how the body handles Ringer's acetate solution. During volume loading, a much greater fraction of the infused fluid was retained in the blood than the 20–25% commonly indicated in medical textbooks. In fact, 20% was not attained until 30 min after infusion, and some of this dilution might have been caused by blood sampling.

The percentage of infused fluid that remained in blood was also dependent on the infusion rate. This finding can be understood better by expressing haemodilution as a change in blood volume, where it becomes apparent that the load–volume relationship should be described by an exponential function rather than by a straight line. The steady-state level corresponded to expansion of blood volume by approximately 550 ml in our resting healthy females. This finding is of interest when Ringer's solution is given very rapidly, such as when volume loading is performed before induction of spinal or extradural anaesthesia. As the volume effect of Ringer's solution is the main purpose of the load, it would seem advisable to slow down an i.v. infusion given very rapidly when steady state is approached. To continue the infusion at a high rate confers no benefit.

These observations suggest that the disposition of a volume load given by i.v. infusion is usually described in oversimplified terms. A mathematical model is needed to analyse more accurately and simulate what happens to the fluid under different conditions. The model used here was developed to describe a dynamic situation. The molecules used to estimate the dilution are already present in the circulation and no radioactive tracer is needed. It is assumed that powerful homeostatic forces act to restore any deviation of fluid spaces to an optimal "target volume" by means of dilution-dependent elimination of fluid. The validity of this view is supported by this study, as elimination of fluid predicted by the model correlated well with urine volume measured.

One- and two-fluid space models were applied to the data. Evidence of expansion of both central and peripheral fluid spaces was found primarily in experiments where a relatively small fraction of the infused volume (mean 48%) was passed during the 2-h follow-up period. In these cases, the volume of the central fluid space was very close to the estimated plasma volume. In most experiments, however, the two-fluid space model offered marginal improvement of the residual error resulting from the curve-fitting procedure. This implies that Ringer's solution, from a kinetic point of view, usually diluted a single well-stirred fluid space. In these experiments, we found more prompt renal excretion of the infused fluid (mean 75%) than in experiments where the two-volume model significantly decreased the residual error. The fact that experiments where the fluid was handled according to VOFS1 were accompanied by both a larger model-predicted fluid loss and a larger urine volume than VOFS2 supports our view that our fluid space models have a physiological basis.

The current view of the disposition of crystalloid solutions such as Ringer's solution is that they are distributed throughout the whole extracellular volume space, which is approximately 12 litre in adult females. However, this study showed that dilution of blood reflected an expandable volume of only 5 litre. This is compatible with the view that Ringer's solution is sequestered in the entire extracellular fluid space while expanding only 40% of it. This finding can probably be explained by a lower compliance for volume expansion in some tissue regions. In fact, the interstitial fluid space is often conceived as a two-phase gel[8]; one phase is difficult to expand because it has a high density of collagen, elastin and glycosaminoglycan, the other phase expands more easily because the density of these macromolecules is lower.

Our results showed that the kinetic model is suitable for further development, as similar results were obtained when the fluid was infused at different rates and also when a different dose was given. The fastest administration of Ringer's solution was the only exception. The large target volume and the symptoms associated with the highest infusion rate probably reflect the fact that areas with lower compliance for accumulation of fluid were also expanded.

To the anaesthetist, the expandable (target) volume is a useful concept as the dilution of the expandable fluid space indicates how much fluid remains in the body during and after i.v. infusion. The volume of the extracellular fluid should apparently not be used for such estimations. Similarly, the rate of urine excretion is the product of $k_r$ and plasma dilution, although we also have to consider a small basal diuresis.

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# The lumbar extradural structure changes with increasing age

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## Summary

We have examined the extradural space using a flexible extraduroscope in 74 patients undergoing extradural anaesthesia at the L2–3 interspace. Extraduroscopy showed that the extradural space becomes widely patent and the fatty tissue in the extradural space diminishes with increasing age. We postulate that these age-related structural changes may affect the spread of local anaesthetic in the extradural space. (*British Journal of Anaesthesia* 1997; **78**: 149–152).

**Key words**
Anaesthetic techniques, extradural. Measurement techniques, extraduroscopy. Anatomy, extradural space. Age factors.

Many investigators have described the effects of ageing on extradural dose requirements in lumbar extradural anaesthesia.[1–4] Some authors have reported a reduction in lumbar extradural dose requirements with age,[1–3] while others have found that age has little or no effect on the spread of lumbar extradural anaesthesia.[4] However, the reasons for the increase in cephalad spread of extradural analgesia in the elderly have not been investigated thoroughly. Several age-related factors may contribute to the extensive spread of local anaesthetics, especially in the elderly, including arteriosclerosis, decreased neural population[5 6] and increased compliance of the extradural space.[7] The changes in the structure of the extradural space with increasing age may affect cephalad spread of local anaesthetics in the extradural space. Because extraduroscopy can provide a clear view of the lumbar extradural space,[8 9] we used this technique to investigate the effects of age on the structure of the extradural space.

## Patients and methods

This study was approved by our local Ethics Committee and informed consent was obtained from all patients. We examined the lumbar extradural space using a flexible fibrescope in 76 patients undergoing lumbar extradural anaesthesia for a variety of surgical or therapeutic procedures, including hysterectomy, oophorectomy, knee arthroscopy, total knee arthroplasty, total hip arthroplasty, extracorporeal shock-wave lithotripsy, transurethral resection of the prostate and transurethral resection of bladder tumours. Pregnant women and patients with a history of prior extradural anaesthesia, neurological disease or abnormalities of the vertebral column were excluded. Each patient was premedicated with hydroxyzine 25–50 mg. The patient was then placed in the right lateral decubitus position on a horizontal operating table. A 17-gauge Tuohy needle was introduced at the L2–3 interspace using the paramedian technique. The extradural space was identified using the loss-of-resistance method with 5 ml of air. When no cerebrospinal fluid or blood flowed from the needle, the patient underwent examination of the lumbar extradural space with a flexible fibrescope measuring 0.7 mm in diameter (MS-501, Igarashi Ika Kogyo Co., Tokyo, Japan) which was connected to a television monitor system (FV-2000E, Igarashi Ika Kogyo Co., Tokyo, Japan). The extraduroscope was introduced approximately 10 cm in a cephalad direction into the extradural space via the Tuohy needle. No more air was injected after insertion of the extraduroscope in each patient. If paraesthesia or resistance were noted during insertion of the extraduroscope, no attempt was made to advance the extraduroscope through the area of resistance. Consequently, two patients in whom the extraduroscope could not be advanced more than 5 cm cephalad were excluded from analysis. Extraduroscopic findings were recorded continuously on a video recorder during the examination in each patient. After extraduroscopic examination, an extradural catheter (external diameter 0.85 mm; B. Brown, Bethlehem PA, USA) was inserted 5 cm cephalad into the extradural space and the patient was then placed in the supine position. All procedures were performed by the same anaesthetist. Patients received local anaesthetic via the catheter during the planned therapeutic or surgical procedure, with or without general anaesthesia, used in combination.

The extraduroscopic findings in our 74 patients were analysed by two independent investigators who were blinded to the patients' medical histories. Extraduroscopic findings were divided into five

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categories for analysis: patency of the extradural space, amount of fatty tissue, amount of fibrous connective tissue, degree of vascularity and blood vessel trauma at the tip of the Tuohy needle. The patency of the extradural space was scored using the following grading system: 1=extremely narrow, 2=patent and 3=widely patent. The other four findings were scored using the following grading system: 1=none, 2=moderate and 3=extensive. When a discrepancy between two observers in each finding was noted, this difference was resolved by a third experienced investigator to reach consensus.

Statistical analyses were carried out using a statistical software package (StatView V4.02, Abacus Concepts, CA, USA) on a personal computer (Macintosh Quadra 650, Apple Computer, Inc., CA, USA). The relationship between age and each extraduroscopic finding was analysed by Spearman's correlation coefficient by rank. Mean age in each grade of the extraduroscopic finding was analysed by the Kruskal–Wallis test and Mann–Whitney's *U* test. $P<0.05$ was considered statistically significant.

## Results

Mean age, height and weight were 51 (range 23–81) yr, 157 (SD 8) cm and 56 (9) kg, respectively (table 1).

Extraduroscopic examination (table 2) revealed significant correlations between age and the patency of the extradural space ($\rho=0.33$, $P=0.02$) and the amount of fatty tissue ($\rho=-0.28$, $P=0.004$). Amount of fibrous connective tissue, degree of vascularity and blood vessel trauma were not related to age. None of the extraduroscopic findings in this study showed correlations with height, weight, body mass index or body surface area. With regard to patency, mean age was significantly higher in patients who scored 3 than in patients who scored 1 or 2 (table 3). With regard to the amount of fatty tissue, mean age was significantly lower in patients who scored 3 than in patients who scored 1 or 2. Blood vessel trauma at the site of the Tuohy needle in the extradural space was observed in 21 (28%) patients, all of whom were scored as grade 2, on the fatty tissue, dura mater or periosteal layer. There was no productive or massive bleeding which occupied the extradural space. None of the blood vessels was injured by the extraduroscope at a site distant from the Tuohy needle.

Figure 1 shows typical extraduroscopic findings in elderly patients. The extradural space in a 77-yr-old man was observed as a widely patent canal (fig. 1A). The grey membranous structure on the left was identified as the dura mater and the right part of the canal was identified as the periosteal layer. Fibrous

*Table 1* Patient data (mean (SD) [range])

| | |
|---|---|
| Age (yr) | 51 [23–81] |
| Height (cm) | 157 (8) [139–178] |
| Weight (kg) | 56 (9) [41–81] |
| Body mass index (kg $m^{-2}$) | 23 (3) [18–31] |
| Body surface area ($m^2$) | 1.56 (0.15) [1.28–1.98] |

*Table 2* Relationship between age and each extraduroscopic finding

| | Spearman's rank correlation test |
|---|---|
| Age *vs* patency of extradural space | $P$=0.02 ($\rho$=0.33) |
| Age *vs* amount of fatty tissue | $P$=0.004 ($\rho$=−0.28) |
| Age *vs* amount of fibrous tissue | ns |
| Age *vs* vascularity | ns |
| Age *vs* blood vessel trauma | ns |

*Table 3* Mean (range) age (yr) in each grade of the extraduroscopic finding. $^*P<0.05$ compared with other grades of the same extraduroscopic finding

| | Score | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Patency | 47 (32–74)<br>(*n*=20) | 49 (23–80)<br>(*n*=40) | 66 (32–81)*<br>(*n*=14) |
| Amount of fatty tissue | 65 (32–81)<br>(*n*=9) | 57(23–80)<br>(*n*=26) | 44 (27–76)*<br>(*n*=39) |
| Amount of fibrous tissue | 54 (23–81)<br>(*n*=35) | 49 (27–77)<br>(*n*=33) | 44 (29–67)<br>(*n*=6) |
| Vascularity | (*n*=0) | 52 (23–81)<br>(*n*=63) | 44 (27–71)<br>(*n*=11) |
| Blood vessel trauma | 53 (23–81)<br>(*n*=53) | 46 (23–81)<br>(*n*=21) | (*n*=0) |

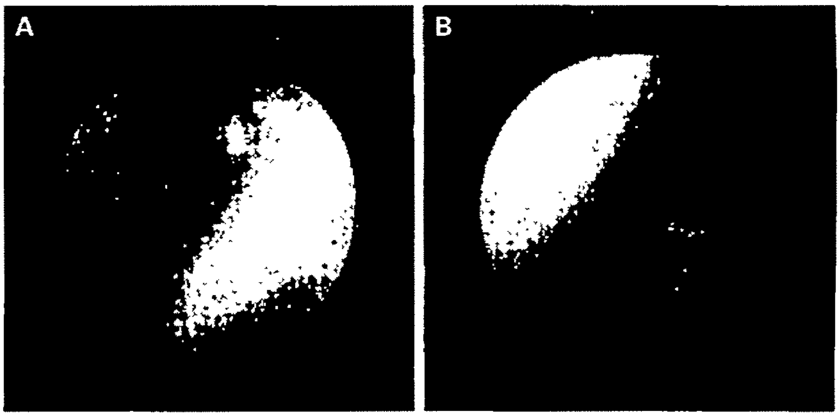

*Figure 1* Photographs obtained via the extraduroscope in a 77-yr-old man The extradural space is observed as a widely patent canal (A). Fatty tissue is seen to have been torn from the dura mater by the air injected into the extradural space as the extraduroscope is advanced (B) Fibrous connective tissues extend across the patent canal. In this patient, the patency of the extradural space, amount of fatty tissue, amount of fibrous connective tissue and degree of vascularity were scored as 3, 2, 3 and 1, respectively

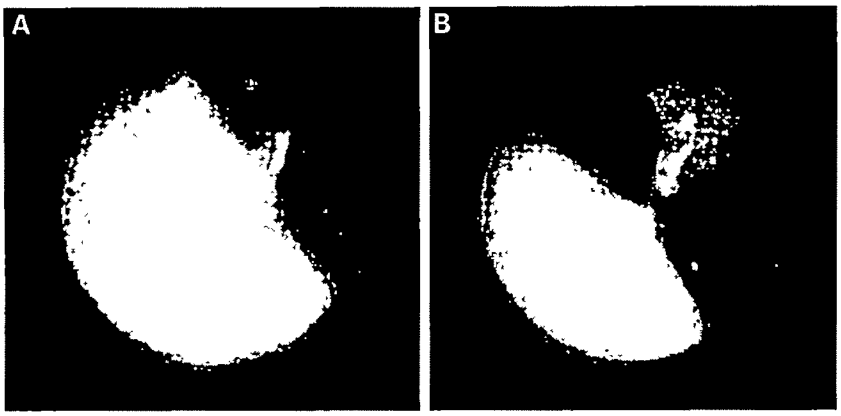

*Figure 2* Photographs obtained via the extraduroscope in a 26-yr-old man. The extradural canal appears to be extremely narrow because of the presence of a large amount of fatty tissue (A) The fatty tissue is seen to be under tension and tightly adherent to the dura mater or the periosteal layer beyond the fibrous connective tissue (B). In this patient, the patency of the extradural space, amount of fatty tissue, amount of fibrous connective tissue and degree of vascularity were scored as 2, 3, 3 and 2, respectively.

connective tissue was seen between the dura mater and the periosteal layer. In the same patient, fatty tissue was observed in the extradural space as the extraduroscope was advanced (fig. 1B). The left part of the canal was identified as the dura mater with its associated blood vessels and the right part of the canal was identified as fatty tissue associated with the periosteal layer. In this region, fatty tissue was seen to have been torn away from the dura mater by the air injected into the extradural space and fibrous connective tissue was seen extending across the patent canal. In this patient, patency of the extradural space, amount of fatty tissue, amount of fibrous connective tissue and degree of vascularity were scored as 3, 2, 3 and 1, respectively.

Figure 2 shows typical extraduroscopic findings in young patients. A narrow extradural space created by the injected air is seen in the right, lower part of the photograph obtained in a 26-yr-old man (fig. 2A). The left part of the canal appears as a white membrane with associated blood vessels and was identified as the dura mater. The outer area on the right side of the photograph was identified as fatty tissue with blood vessels. The extradural canal appeared to be very short and narrow because of the presence of a large amount of fatty tissue (fig. 2B). The fatty tissue was seen to be under tension and tightly adherent to the dura mater or the periosteal layer beyond the fibrous connective tissue. In this patient, the patency of the extradural space, amount of fatty tissue, amount of fibrous connective tissue and degree of vascularity were scored as 2, 3, 3 and 2, respectively.

We encountered no accidental dural punctures and observed no signs of persistent neurological injury in any of our patients.

## Discussion

In this study, extraduroscopic examination revealed that the amount of fatty tissue was reduced and the extradural space became widely patent with increasing age. We postulate that the amount of fatty tissue in the lumbar extradural space may play an important role in determining the patency of the extradural space, thereby affecting the longitudinal spread of anaesthetic solutions in the elderly.[1-3]

We found that the patency of the extradural space, after injection of 5 ml of air into the extradural space, became greater with increasing age. Our results on the patency of the extradural space may be related to the fact that the compliance of the extradural space increases with advancing age.[7]

Another extraduroscopic finding was that the amount of fatty tissue was related inversely to increasing age. This may be one reason for the changes in patency of the extradural space in the elderly. As the fatty tissue degenerates with advancing age, the extradural space becomes more compliant, resulting in the observed changes in the patency of the extradural space. In addition, our results demonstrated that the extradural space in young patients was packed tightly with rigid fat[10] and showed low compliance.

Connective tissues other than fatty tissue were observed as strands or membranes in the extradural space and were not found to be related to age. These connective tissues are found between the fatty tissue, dura mater and periosteal layer. Although these connective tissues were thought to be important factors related to compliance of the extradural space, we did not find age-related differences in fibrous connective tissues. Because these fibrous connective tissues were more fragile than the fatty tissue, they may have been stretched and broken by the air introduced into the extradural space. If the amount of air introduced into the extradural space was more or less than 5 ml, it may be possible to demonstrate statistically significant changes in the amount of fibrous connective tissue with increasing age.

In assessing the results of this study, we must consider several factors that may have affected our results. The extradural space was observed after introducing a small amount of air. The extradural space is sometimes described as a potential space, rather than a true cavity.[9 11 12] The introduction of air may therefore have affected our extraduroscopic findings, expanding the extradural space and stretching the connective tissues. However, in our study, all patients received identical extradural punctures and the effects of air introduced into the extradural space should have been comparable in all cases. Therefore, we believe that this factor had no influence on our comparative findings.

We observed fatty tissue in a segmental distribution in the extradural space as the extraduroscope was advanced in a cephalad direction. That the extradural fatty tissue is divided into segments by interposed laminae in the lower thoracic and lumbar regions has been demonstrated by sagittal midline magnetic resonance imaging.[13] In this study, extradural structures were observed mainly from the point where the fatty tissue ceased to exist. We did not divide our extraduroscopic findings into two separate categories based on the presence or absence of fatty tissue because the patency of the extradural space tended to be similar regardless of the presence of fatty tissue.

In the lower thoracic and lumbar segments, it has been suggested that the extradural space is divided transversely into three compartments: anterior, dorsal and dorsolateral.[14] Unfortunately, we were not able to determine which of the three compartments of the extradural space was observed in this study. In some cases the extraduroscopic findings showed the compartments of the extradural space to be incompletely separated by thin and fragile membranes. Our extraduroscopic procedures were performed by the same anaesthetist and the tip of the Tuohy needle was introduced into the extradural space as precisely as possible in the midline. However, differences between the three compartments in terms of extraduroscopic findings have not yet been clarified, and these differences may have affected our findings.

Several technical problems were encountered during the procedure. Nerve root irritation during insertion of the extraduroscope may be related to technical problems with extradural puncture. The cord or nerve roots may be compressed during insertion of the extraduroscope, which is more rigid than the extradural catheter. Although extradural punctures were performed using the same procedures employing the paramedian technique, the angle of the needle relative to the dorsal plane of the skin may have varied from patient to patient. We postulate that the greater the cephalad angle of the needle relative to the dorsal plane of the skin, the lower the incidence of nerve root irritation. Indeed, in patients who experienced nerve root irritation during insertion of the extraduroscope, repeat attempts with a greater needle angle made it possible to insert the extraduroscope into the extradural space without eliciting nerve root irritation. Therefore, the cephalad angle of the Tuohy needle relative to the dorsal plane of the skin appears to be a very important consideration in performing extraduroscopy without nerve root irritation. Although none of our patients who experienced nerve root irritation suffered permanent neurological injury, care should be taken not to damage the nerve roots or cord when irritation is encountered during extraduroscopic examinations.

We observed blood vessel trauma induced by the introduction of the Tuohy needle into the extradural space in approximately 25% of all patients. Arteriosclerosis is seen frequently in the elderly, and the incidence of blood vessel trauma might therefore be expected to increase with advancing age. However, the incidence of blood vessel trauma by the tip of Tuohy needle was not found to be related to age. Blood vessel trauma was observed on the fatty tissue, dura mater and periosteal layer by the tip of Tuohy needle in the extradural space. However, we observed no productive or massive bleeding which was filled with the extradural space. Although we sometimes experience intravascular migration of an extradural catheter in clinical practice,[15 16] it remains unknown in which vessels the extradural catheter is misplaced.

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# Do anxiety or hypocapnia predispose to apnoea after induction of anaesthesia?†

G. B. DRUMMOND AND N. M. M. EL-FARHAN

## Summary

We have studied the incidence of apnoea after induction of anaesthesia in patients allocated randomly to receive a standardized dose of either propofol or etomidate. We measured anxiety before operation with a standard questionnaire and end-tidal carbon dioxide concentration from a mask during breathing 35% oxygen, before induction of anaesthesia. Respiration was measured by pneumotachograph and impedance pneumograph. There was no significant relationship between anxiety score and end-tidal carbon dioxide concentration before operation. Patients given propofol ($n=26$) received a median dose of 157 mg over 70 s, and 17 became apnoeic (median duration 24 s, quartile values 0, 76). Apnoea was more severe in patients whose preoperative end-tidal carbon dioxide value was less than the median value (median duration of apnoea 61 s compared with 10 s; $P<0.05$). Patients given etomidate ($n=25$) received 16.2 mg in 57 s, which was a significantly smaller fraction of the calculated dose requirement, and had significantly less apnoea: eight became apnoeic (median duration 0 s, quartile values 0, 23 s). There was no relationship between apnoea and end-tidal carbon dioxide concentration in these patients. Anxiety did not relate to the incidence of apnoea with either induction agent. We conclude that apnoea after induction of anaesthesia with propofol is more likely if hypocapnia is present but we could not relate apnoea or hypocapnia to anxiety in the ward before operation. (*Br. J. Anaesth.* 1997; **78**: 153–156)

**Key words**
Complications, apnoea. Ventilation, apnoea. Anaesthetics i.v., propofol. Anaesthetics i.v., etomidate. Carbon dioxide, hypocapnia. Psychological responses

Apnoea is frequent after introduction of anaesthesia with i.v. agents, and more likely with propofol than with other agents.[1] Propofol depresses the ventilatory response to hypoxia,[2] but in some circumstances apnoea can also be caused by a combination of hypocapnia and sedation: for example it can be caused by voluntary hyperventilation in association with nitrous oxide inhalation.[3] Patients receiving preoxygenation may be encouraged to hyperventilate or may hyperventilate because they are anxious, and hence become hypocapnic. We tested the hypothesis that anxiety and hypocapnia before operation would predispose to apnoea and studied the effects of two agents that are known for their different effects on respiration, propofol which causes more apnoea[1] and etomidate less, in comparison with other agents.[4]

## Patients and methods

After obtained local Ethics Committee approval and written informed consent, we studied women undergoing gynaecological procedures under general anaesthesia as day patients. We excluded patients who were more than 40% of their expected weight, had clinically significant cardiorespiratory disease or who were receiving medication that could alter anxiety or respiratory responses. We did not exclude those who were in early pregnancy. Between 30 min and 2 h before the anaesthetic, we assessed each patient's anxiety using a standardized questionnaire consisting of 12 statements, with the response to each question graded from "not at all" to "extremely" in five categories. The statements were both positive (e.g. "I feel I can cope") and negative (e.g. "I want to escape from here") so that the categorical response required more careful thought. The categories were marked from 1 (least anxious) to 5 (most anxious) and summed so that the score was between 12 (least anxious) and 60 (most anxious).

To allow anaesthetic induction to be as standard as possible, and compare the induction agents, we estimated the induction dose required for each patient so that by giving this estimated dose at a steady rate each patient should receive an induction dose of the agent over the same time. We noted height and weight of the patients and measured skinfold thickness at the biceps, triceps, subscapular region and suprailiac regions with standard methods to allow estimation of lean body mass.[5] Using age

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and lean body mass we predicted the clinical induction dose of thiopentone using regression data from Avram and co-workers,[6] with the equation:

$$\text{dose (mg)} = 282 + 1.6 \text{ lean mass (kg)} - 1.78 \text{ age (yr)}$$

From this thiopentone dose, the equivalent induction dose for propofol was obtained using a relative potency of 0.625.[7] For etomidate we used a ratio of 0.038. These doses of propofol and etomidate, given over 100 s, provide a median induction dose for similar patients (unpublished data). We diluted 1.4 times the estimated induction dose in 40 ml, with 0.9% sodium chloride containing 1 ml of 0.5% lignocaine solution. At induction of anaesthesia this was given as 0.4 ml $s^{-1}$ so that a median induction dose was given in approximately 70 s and further agent was available in the syringe if necessary for patients who required more than the median amount. Randomization was with sealed envelopes in blocks of 20.

No premedication was given. When the patient came to the anaesthetic room an i.v. cannula was inserted in one hand and a two-electrode impedance pneumograph was attached using disposable silver–silver chloride ECG electrodes placed on each side of the chest in the midaxillary line at the level of the nipples. Standard electrodes for ECG monitoring, non-invasive arterial pressure cuff and a finger probe pulse oximeter were attached. No arterial pressure measurements were made during the measurements. A well fitting mask, with an inflatable pneumatic rim (Respironics), was applied to the face and the patient's head extended to allow a clear airway to be maintained. The mask was fitted with a sampling port which was connected to a sidestream capnometer (Datex Oxycap), calibrated at the start and end of the study with the manufacturer's standard gas. The mask was connected to a pneumotachograph and a T-piece system supplied with a Venturi oxygen device that gave 35% oxygen: the other limb of the T-piece was open to room air. Pneumotachograph pressure was measured with a differential transducer (Furness micromanometer) and the flow and pneumograph signals passed to a laptop computer for digitizing and storage using a commercial logging and analysis package (Oxcams Cardas). The patient was then given a solid steel cylinder, 10 cm long and 1.25 cm in diameter, to hold between the thumb and first finger of the hand that did not have the i.v. cannula, and asked to hold it without letting it drop.

After the patient had been breathing from the system for approximately 2 min she was asked to exhale to obtain a good expiratory plateau value for end-tidal carbon dioxide concentration and this value was noted. When respiration had become regular again and satisfactory signals of flow and pneumograph were present on the computer display, the induction agent was injected at 0.4 ml $s^{-1}$ until the patient dropped the weight, when injection stopped and the time was recorded on the computer. If there was no flow signal, then the mask was kept in place until respiration re-started. The impedance signal was observed to see if there was obstructive apnoea, with absent flow but continued chest wall movements, in which case the head and neck were moved to obtain a clear airway. The mask was kept in place until respiration re-started and then removed to allow the anaesthetic to be continued. The digitized record was replayed later. Apnoea was defined as the absence of inspiratory flow for more than 10 s: if apnoea occurred, the times of cessation and restarting respiration were noted. Summary values for apnoea duration in the groups were calculated using zero values for those subjects who did not stop breathing.

After the patient had returned to the ward, another measurement was made of end-tidal carbon dioxide concentration between 1 and 2 h after the procedure. Analgesics used in the operative and postoperative periods, which were not standardized, were noted.

The relationship between the incidence and duration of apnoea, preoperative anxiety score, end-tidal carbon dioxide concentration and induction agent was investigated with scatter plots. The incidence of apnoea was tested using the chi-square test and the severity of apnoea compared between agents, and within subgroups, using the Mann–Whitney test, with Minitab version 8.2 running in MS-DOS version 6.2. $P<0.05$ was taken as significant. The distribution of many of the variable values was not normal and they are summarized as median (interquartile) values.

## Results

Of 56 patients who agreed to the study, 54 were allocated randomly to treatment (six were asked and declined to take part). Patient details are shown in table 1. There were no differences between groups in age, height, weight, percentage body fat, preoperative anxiety scores or end-tidal carbon dioxide values.

The median dose of propofol given was 158 (140,182) mg and induction time was 67 (59, 77) s. This was significantly greater than the induction time for the etomidate group (57 (48, 64) s; dose administered 16 (14.5, 17.6) mg). Because the agents were given at a rate set by the predicted dose for each patient, the different induction times indicate a significant difference between the proportion

*Table 1* Patient details (median (quartile values) or numbers)

| | Propofol group | Etomidate group |
|---|---|---|
| *n* | 26 | 25 |
| Age (yr) | 31 (28–39) | 34 (26–41) |
| Height (cm) | 160 (158–163) | 163 (158–169) |
| Weight (kg) | 64 (60–70) | 64 (57–74) |
| % Body fat | 37 (34–40) | 36 (32–40) |
| Anxiety score | 23 (18–29) | 25 (19–29) |
| Preoperative end-tidal $CO_2$ (kPa) | 4.4 (4.3–4.7) | 4.8 (4.5–5.3) |
| Dose prediction (mg) | 181 (173–187) | 22 (21–23) |
| Dose administered (mg) | 158 (141–182) | 16 (14.5–17.6) |
| Dose given/dose predicted | 0.87 (0.78–1.05) | 0.75 (0.66–0.83) |
| Induction time (s) | 67 (60–77) | 57 (48–64) |
| Apnoea (*n*) | 17 | 8 |
| Apnoea (s) (all patients) | 24 (0–77) | 0 (0–23) |
| Postoperative end-tidal $CO_2$ (kPa) | 4.7 (4.1–5.5) | 4.8 (4.5–5.3) |

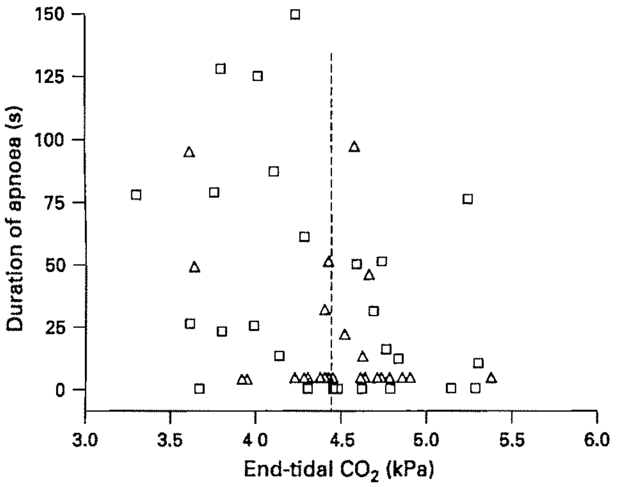

*Figure 1* Relationship between apnoea, taken as absence of breathing for more than 10 s, and preoperative end-tidal carbon dioxide ($CO_2$) values in patients receiving propofol (□) or etomidate (△) (these symbols are offset upward to improve clarity).

of predicted dose given; for propofol 0.87 (0.77–1.05) and for etomidate 0.75 (0.66, 0.83) ($P<0.01$).

There was no relationship between preoperative anxiety score and end-tidal carbon dioxide values before operation.

There was a significant difference in the incidence and duration of apnoeas in patients who received propofol (17 apnoeas, median duration of apnoea 24 (0, 77) s) compared with the etomidate group (eight apnoeas, median duration 0 (0, 23) s) ($P<0.05$). Figure 1 shows the relationship between apnoea duration and preoperative end-tidal carbon dioxide values. Because the relationship between these values was not linear, we classified patients into those whose preoperative end-tidal carbon dioxide concentration was greater, and less than or equal to the median: we then compared duration of apnoea in the low and high end-tidal carbon dioxide groups. In patients who received propofol, apnoea was significantly greater in the 13 patients who had smaller carbon dioxide values (61, 18–146 s) compared with those who had larger carbon dioxide values (10, 0–40 s) ($P=0.0167$). This relationship was not found in patients who received etomidate (0, 0–41 and 0, 0–14 s for the two groups, which contained 12 and 13 patients, respectively) ($P=0.767$).

Most patients received a variety of analgesics, including long- and short-acting opioids, either during or after the procedures, and no relationship was found between postoperative end-tidal carbon dioxide values or changes in values before and after operation, with any other variable. Postoperative values were obtained 25–95 min after recovery from anaesthesia. One value could not be obtained for technical reasons, but for the remainder, median end-tidal carbon dioxide values after operation were 4.8 (4.2–5.3) kPa whereas they were 4.4 (4.1–4.7) kPa before the procedure ($P<0.01$). There was no difference in carbon dioxide values after operation in patients who received propofol and those who received etomidate.

## Discussion

Apnoea is less frequent when propofol is given slowly[8] whereas slow injection of other induction agents does not seem to affect the incidence of apnoea.[4] As we wished to compare the two agents, we used a method that should have allowed us to give the induction dose of both agents in the same time. We used estimates of potency derived in the same type of patient, where the induction dose was given over approximately 80 s. Injection time was decreased slightly in this study to approximately 70 s. We did so to more closely simulate the rate of injection that is used commonly in clinical practice and we wished to allow apnoea to become apparent so that we could investigate the relevant factors associated with it. However, the estimates were greater than necessary, significantly so for etomidate, and therefore the injection times were significantly different. However, the differences were small (12% of the dose estimate) and we do not consider that the difference in time taken for injection (57 *vs* 66 s) affected the comparability of the effects of the agents, particularly as both were given to the same end-point.

We used preoxygenation to avoid the confounding effect of hypoxia, which may contribute to restoration of breathing after apnoea has occurred, but avoided using 100% oxygen because it may alter cerebral blood flow and thus affect respiration.[9] Although propofol depresses the ventilatory response to hypoxia[2 10] there are no definitive reports that preoxygenation can prolong the duration of apnoea caused by propofol, and a decrease in ventilation in response to hyperoxia can be found to persist during propofol anaesthesia.[11] The depressant effects of propofol on ventilatory responses to carbon dioxide are also significant and prolonged.[12] Consequently, our finding that propofol caused apnoea, and etomidate did not, was expected, and we have concentrated on the features of the apnoea in this group of patients.

We have used the questionnaire for anxiety in previous studies and found it satisfactory. As suggested by Millar and co-workers, it describes anxiety in terms that most patients find familiar.[13] These workers found three different methods of measurement of equivalent efficacy, and we consider that our questionnaire is similar. However, we found that anxiety measured in this way could not be related to preoperative end-tidal carbon dioxide concentration or to the incidence of apnoea. Anxiety may have increased between completing the form and starting the induction of anaesthesia, to a different degree in different subjects, thus invalidating this measure as a test of the initial hypothesis.

We measured end-tidal carbon dioxide using a mask, which is less accurate than the use of a mouthpiece, but we were able to assess the size of the expired breath and are confident that measurements in these relatively young and healthy subjects were a good index of $Pa_{CO_2}$. However, we did not control or standardize analgesic administration (which varied considerably according to the procedure undertaken) and hence are not confident that the values of end-tidal carbon dioxide that we obtained after operation were of value, although we had hoped that the change from before to after operation could have been an index of those patients who were hypocapnic before the procedure, by relating the carbon dioxide value to their resting value.

There was no clear linear relationship between preoperative carbon dioxide concentration and apnoea. However, it was evident that hypocapnia was associated with more frequent and prolonged apnoea after propofol, whereas the less frequent apnoeas after etomidate could not be related to hypocapnia. We propose that the drive to respiration from wakefulness and anxiety have reduced arterial and brain carbon dioxide values well below those necessary to stimulate respiration, and after loss of consciousness these values have to increase sufficiently before regular respiration starts again. We attempted to minimize upset to the patient from the use of the mask, and it is likely that the effects were similar to a routine anaesthetic, and consequently we are confident that our findings reflect the clinical situation. Although other manoeuvres have been suggested as helpful in reducing the likelihood of apnoea after induction of anaesthesia, such as slow administration of propofol and vital capacity breaths before induction,[14] we suggest that manoeuvres to limit the development of hypocapnia may be useful if apnoea is troublesome.

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# Comparison of induction and recovery between sevoflurane and halothane supplementation of anaesthesia in children undergoing outpatient dental extractions

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## Summary

We have compared sevoflurane and halothane in a double-blind controlled study for supplementation of nitrous oxide and oxygen anaesthesia in 80 children undergoing dental extraction as outpatients. Induction of anaesthesia was more rapid in those who received sevoflurane compared with those who received halothane (89 s compared with 127 s for loss of eyelash reflex). In both groups, mean duration of administration of anaesthesia was less than 4 min. Those who received sevoflurane were slower to awaken (167 s compared with 102 s), although discharge times from hospital were similar. The incidence of complications during induction and maintenance was low in both groups and return to normal appetite and activity occurred in the majority of children on the same day. More children who received halothane suffered nausea after leaving hospital. We conclude that sevoflurane is a suitable alternative to halothane, with more rapid induction of anaesthesia, but in these short procedures, awakening time was slower than after halothane. (*Br. J. Anaesth.* 1997; **78**: 157–159)

**Key words**

Anaesthesia, paediatrics. Anaesthetics volatile, halothane. Anaesthetics volatile, sevoflurane. Surgery, dental. Children.

The majority of patients who require anaesthesia for dental extraction are children who are unwilling to accept needles and request inhalation induction. Rapid induction and swift recovery are desirable characteristics of anaesthesia for these short procedures which are performed on an outpatient basis. The low blood:gas partition coefficient of sevoflurane[1] and its lack of airway irritability suggest that it has many features of the ideal inhalation agent[2] and that it may be preferable to halothane for short procedures in children.[3–9] Although more rapid recovery from anaesthesia with less soluble agents may be anticipated, a previous study[10] comparing isoflurane with halothane did not show this to be the case in paediatric dental outpatients.

We have compared induction, maintenance and recovery from brief anaesthesia when either sevoflurane or halothane was the sole supplement to anaesthesia with nitrous oxide and oxygen in unpremedicated children undergoing outpatient dental extractions.

## Patients and methods

After obtaining local Ethics Committee approval and written parental consent, we studied 80 healthy children, not receiving any medication, aged 5–12 yr, undergoing dental extraction as outpatients for which inhalation induction of anaesthesia was requested. Children were allocated randomly to one of two groups to receive either sevoflurane or halothane supplementation of 66% nitrous oxide in oxygen, in approximately equipotent inspired concentrations.[2 11]

No premedication was used. Induction of anaesthesia was by inhalation of 2% sevoflurane or 0.75% halothane and 66% nitrous oxide in oxygen for five breaths before maintenance with 4% sevoflurane or 1.5% halothane until the teeth had been extracted. The vaporizer settings were controlled behind a screen by a second anaesthetist, such that the administering anaesthetist was unaware which volatile agent was being given. Anaesthesia was given with the child sitting in the dental chair, via a close-fitting nasal mask using a Mapleson A system with active scavenging. Routine digital pulse oximetry was used to monitor oxygen saturation. The times at which loss of eyelash reflex occurred and at which jaw tone became sufficiently relaxed to permit insertion of a dental gag and mouth pack were recorded. These times and the presence or absence of complications were assessed by the administering anaesthetist.

Recovery from anaesthesia was assessed by the time taken from discontinuation of anaesthesia until the child opened his/her eyes. In the recovery room, experienced recovery nurses, who were also unaware of the agent used, recorded when the child was able to stand unaided without swaying and was able to walk in a straight line. The presence or absence of nausea, vomiting, shivering, headache and coughing

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in recovery and when the child was ready to leave hospital were also recorded.

Return to normal activity and normal appetite in addition to the presence or absence of headache, nausea, vomiting, dizziness, muscle aches and bad dreams were sought using a questionnaire completed and returned by the accompanying parent.

Statistical comparisons of patient characteristics, operative details, and induction and recovery times were made by unpaired Student's *t* test. Complications during induction of anaesthesia, while recovering in hospital and after going home were compared by chi-square test.

## Results

Both groups were comparable in age, weight, number of teeth extracted, duration of administration of anaesthesia and duration of surgery (table 1). Induction of anaesthesia was significantly shorter ($P<0.05$) in children who received sevoflurane in whom the mean time to loss of eyelash reflex was 89 s compared with 127 s in those who received halothane (table 1). There were notably few airway complications during induction and maintenance of anaesthesia (table 2). Although movement was noted in some children, this did not interfere with dental extraction.

Mean duration of administration of anaesthesia was similar in both groups and was less than 4 min (table 1). While those children who received halothane awakened significantly more rapidly than those who received sevoflurane, there was no difference in the times taken to stand without swaying and to walk in a straight line unaided. The times at which the children were considered ready for discharge from hospital were similar in both groups.

*Table 1* Patient characteristics, clinical data and induction and recovery times for sevoflurane and halothane anaesthesia (mean (SD or range)). * $P<0.05$ (unpaired Student's *t* test)

| | Sevoflurane ($n$ = 40) | Halothane ($n$ = 40) |
|---|---|---|
| Age (yr) | 8.0 (5–12) | 7.9 (5–12) |
| Weight (kg) | 27.1 (9.2) | 26.5 (8.6) |
| Teeth extracted ($n$) | 3.1 (2.0) | 2.9 (1.9) |
| Duration of anaesthetic administration (s) | 224 (82) | 232 (61) |
| Duration of surgery (s) | 99 (74) | 87 (52) |
| Loss of eyelash reflex (s) | 89 (26) | 127 (32)* |
| Loss of jaw tone (s) | 125 (47) | 146 (31)* |
| Eye opening (s) | 167 (98) | 102 (70)* |
| Standing (min) | 16.8 (4.4) | 14.8 (4.4) |
| Walking (min) | 18.0 (4.9) | 17.0 (5.5) |
| Discharge time (min) | 23.5 (6.4) | 23.7 (6.3) |

*Table 2* Complications during induction and maintenance of anaesthesia (number of children)

| | Sevoflurane ($n$=40) | Halothane ($n$=40) |
|---|---|---|
| Coughing | 1 | 0 |
| Salivation | 1 | 1 |
| Laryngospasm | 2 | 2 |
| Oxygen saturation <95% | 0 | 0 |
| Intraoperative movement | 18 | 13 |

*Table 3* Complications during recovery in hospital (number of children)

| | Sevoflurane ($n$=40) | Halothane ($n$=40) |
|---|---|---|
| Nausea | 10 | 4 |
| Vomiting | 4 | 1 |
| Coughing | 1 | 0 |
| Shivering | 1 | 0 |
| Headache | 10 | 13 |
| Intraoperative recall | 0 | 0 |

*Table 4* Reported complications after discharge from hospital. *$P<0.05$ (chi-square test)

| | Sevoflurane ($n$=31) | Halothane ($n$=32) |
|---|---|---|
| Nausea | 3 | 10* |
| Vomiting | 1 | 3 |
| Headache | 4 | 4 |
| Dizziness | 3 | 5 |
| Bad dreams | 2 | 0 |
| Muscle aches | 5 | 4 |

*Table 5* Postoperative return to normal activity and appetite (number of children)

| | Sevoflurane ($n$=31) | Halothane ($n$=32) |
|---|---|---|
| Normal appetite | | |
| Same day | 24 | 22 |
| Next day | 7 | 9 |
| Later | 0 | 1 |
| Normal activity | | |
| Same day | 22 | 20 |
| Next day | 8 | 12 |
| Later | 1 | 0 |

Headache and nausea were the most frequent complications in the recovery room: there was no significant difference between groups (table 3). After discharge from hospital parents returned questionnaires for 31 children who received sevoflurane and 32 who received halothane. Significantly more children who received halothane suffered nausea after leaving hospital (table 4). The majority of children returned to normal activity and appetite the same day and all except one in each group did so by the following day (table 5).

## Discussion

The most surprising finding was that despite more rapid induction of anaesthesia with sevoflurane, the time to awaken was faster with halothane. This was similar to the finding in a previous study comparing isoflurane and halothane under almost identical conditions.[10] The more rapid induction of anaesthesia with sevoflurane (and isoflurane) is expected from published wash-in curves[12] and is confirmed in clinical practice.[3–9] However, published wash-out curves[12] and initial clinical experience[3–6 8 13] also suggest that early recovery is more rapid after sevoflurane than after halothane. The important difference in our study was the short duration of anaesthesia. At the end of 4 min, children who received sevoflurane were nearer the stage of full saturation than those who received halothane. Consequently, when surgery ended and sevoflurane was discontinued, serum concentrations decreased mainly by excretion whereas for those receiving halothane, considerable scope was available for serum concentrations to decrease by redistribution, in addition to excretion through the lungs. Thus because the volatile agents were discontinued before a state of "plateau" pharmacokinetics had been reached, the relative behaviour of the usually published wash-out curves cannot be expected.

The potentially distressing time for children is during induction of anaesthesia and the fact that sevoflurane reduced the time to loss of eyelash reflex by an average of 38 s (or by 30%) was both statistically and clinically significant. The study was designed to make a direct comparison between sevoflurane and halothane and we accept that higher initial concentrations of sevoflurane or other techniques of induction can further reduce induction times.[14] The absence of respiratory complications on induction is also important to the acceptability of volatile agents for inhalation induction, and both sevoflurane and halothane were well accepted and non-irritant. Notably, there were no episodes of hypoxia.

As in a previous study,[10] the majority of children resumed normal activity and appetite on the same day. This reflects rapid recovery from anaesthesia and minimal effects of minor surgery. The incidence of nausea after leaving hospital was greater in those children who received halothane, but if the results are combined for those who suffered nausea while still in hospital, there was no difference between the agents. The irritant effects of swallowed blood after dental extraction may not make this study comparable with others in children undergoing other types of surgery.

In summary, we found sevoflurane to be a suitable alternative to halothane for dental outpatient surgery in children, having a significant advantage in the speed of induction. The slower awakening time after sevoflurane did not delay discharge from hospital. Recovery to normal activity and appetite was good, and there was a low incidence of adverse effects during induction, maintenance and recovery.

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*British Journal of Anaesthesia* 1997; 78: 160–162

# Plasma bupivacaine concentrations associated with continuous extradural infusions in babies†

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## Summary

The maximum recommended dose for extradural infusions of bupivacaine in children older than 1 month is 0.5 mg kg$^{-1}$ h$^{-1}$ but there are few specific reports of the associated blood concentrations during infusions in babies. Toxic symptoms can occur in children at plasma concentrations of bupivacaine as low as 2 μg ml$^{-1}$. We attempted to measure venous plasma concentrations of total and free bupivacaine in babies aged 3–12 months during extradural infusions given at a rate commonly used in our hospital. We studied eight babies (mean age 33 weeks; mean weight 7.8 kg). After a mean initial dose of 1.2 mg kg$^{-1}$ (range 1.1–1.3 mg kg$^{-1}$), bupivacaine was infused at a mean rate of 0.38 (0.36–0.39) mg kg$^{-1}$ h$^{-1}$ for a mean of 31 (4–44) h. Blood was obtained at 4, 8, 16, 24, 32 and 40 h after starting the infusion and plasma separated by centrifugation. Total plasma bupivacaine concentration was measured using high pressure liquid chromatography (HPLC). Plasma concentrations of total bupivacaine were mostly less than 2 μg ml$^{-1}$. One baby had a concentration of 2.02 μg ml$^{-1}$ at 32 h and showed clear evidence of accumulation of bupivacaine. Babies can accumulate bupivacaine and achieve plasma concentrations above the threshold for toxic side effects, despite infusion rates below the currently accepted maximum. The sample size in our study was small but we believe an extradural infusion rate of 0.375 mg kg$^{-1}$ h$^{-1}$ is probably an absolute maximum for babies younger than 12 months. (*Br. J. Anaesth.* 1997; **78**: 160–162)

**Key words**
Anaesthesia, paediatric. Infants. Anaesthetic techniques, extradural. Anaesthetics local, bupivacaine.

The maximum recommended rate for extradural infusion of bupivacaine in children older than 1 month is 0.5 mg kg$^{-1}$ h$^{-1}$.[1] At the time of this editorial there were no specific reports of blood concentrations of bupivacaine during extradural infusions in babies younger than 12 months. The aim of our study was to measure venous plasma concentrations of both total and free bupivacaine during continuous extradural infusion of bupivacaine 0.375 mg kg$^{-1}$ h$^{-1}$ for the duration of the infusion in babies aged 3–12 months.

## Patients and methods

After obtaining Ethics Committee approval and informed consent from parents, we studied babies, aged 3–12 months, ASA I or II, undergoing major abdominal operations. We excluded babies born before 35 weeks' gestation.

General anaesthesia was induced using a volatile agent or propofol, and neuromuscular block was produced with atracurium or vecuronium. After intubation of the trachea the lungs were ventilated to a normal end-tidal carbon dioxide concentration with oxygen, nitrous oxide and a volatile agent. We then inserted a 23-gauge lumbar extradural catheter using a 19-gauge Tuohy needle (Portex Minipack System) and injected bupivacaine 1.25 mg kg$^{-1}$ (0.25% or 0.5%). Another two doses of 0.6 mg kg$^{-1}$ were given if indicated by changes in heart rate or arterial pressure, up to a maximum total dose during surgery of 2.5 mg kg$^{-1}$. Continuous infusion of 0.25% bupivacaine 0.375 mg kg$^{-1}$ h$^{-1}$ (equivalent to 0.15 ml kg$^{-1}$ h$^{-1}$) was then started for postoperative pain relief. No other analgesics were given during anaesthesia.

A second cannula was inserted into a peripheral vein during anaesthesia for later collection of blood samples and flushed with heparinized saline 10 u. ml$^{-1}$.

After surgery the babies were monitored with an apnoea alarm and pulse oximeter. Assessments by nursing staff of pain and sedation using four-point scoring systems and measurements of heart rate and ventilatory frequency were recorded every hour. Pain was assessed as nil, mild, moderate or severe. Sedation was assessed as awake and alert, occasionally drowsy but easy to arouse, drowsy most of the time but easy to arouse, or somnolent and difficult to arouse.

Approximately 2 ml of blood were obtained from the venous sampling cannula at 4, 8, 16, 24, 32 and 40 h after starting the continuous extradural infusion as long as the extradural infusion was running and the sampling cannula remained patent. Plasma was

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*Table 1* Patient details, operation and loading doses, and subsequent infusion rates of extradural bupivacaine

| Patient No. | Age (wks) | Sex (M/F) | Weight (kg) | Operation | First extradural injection bupivacaine % | First extradural injection bupivacaine Dose (mg kg$^{-1}$) | Additional bolus bupivacaine during surgery % | Additional bolus bupivacaine during surgery Dose (mg kg$^{-1}$) | Rate of extradural infusion 0.25% bupivacaine (mg kg h$^{-1}$) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 18.1 | M | 7.6 | Pyeloplasty | 0.25 | 1.3 | — | — | 0.39 |
| 2 | 19.9 | M | 5.7 | Closure of colostomy | 0.25 | 1.2 | — | — | 0.39 |
| 3 | 45.3 | F | 9.1 | Partial nephrectomy and bilateral re-implantation of ureters | 0.25 | 1.25 | 0.5 | 1.1 | 0.38 |
| 4 | 40 | M | 9.3 | Nephro-uretectomy | 0.5 | 1.1 | — | — | 0.38 |
| 5 | 37 | M | 9.1 | Nephro-uretectomy | 0.5 | 1.3 | — | — | 0.36 |
| 6 | 21.4 | M | 5.6 | Nephrectomy | 0.5 | 1.25 | — | — | 0.38 |
| 7 | 48.1 | M | 7.0 | Bilateral re-implantation of ureters | 0.5 | 1.25 | — | — | 0.39 |
| 8 | 34.3 | M | 9.3 | Re-implantation of ureter | 0.5 | 1.2 | — | — | 0.38 |
| Mean | | | | | | 1.2 | | | 0.38 |

removed by centrifugation, frozen immediately and stored at −20 °C. Total bupivacaine was assayed using a modification of a high pressure liquid chromatography (HPLC) method described for measurement of lignocaine and its metabolites.[2] The sensitivity of the assay was dependent on the volume of plasma and was approximately 0.1 μg ml$^{-1}$ for 100 μl and 0.02 μg ml$^{-1}$ for 500 μl. The coefficient of variation was 5%.

## Results

We studied eight babies. Mean age was 33 weeks (range 18–48 weeks) and mean weight 7.8 (5.6–9.3) kg (table 1). The mean initial dose of bupivacaine given was 1.2 (range 1.1–1.3) mg kg$^{-1}$. One baby was given two additional boluses of 0.5 mg kg$^{-1}$ during surgery (table 1). Extradural bupivacaine was infused at a mean rate of 0.38 (0.36–0.39) mg kg$^{-1}$ h$^{-1}$ for a mean of 31 (4–44) h.

One catheter was removed at 4 h from a baby undergoing laparotomy for closure of a colostomy. The extradural infusion had seemed adequate during surgery but after operation the baby was intermittently distressed. This was attributed to colic and was treated with an infusion of morphine. The other seven babies had renal or ureteric surgery. Their hourly pain scores were nearly all assessed as "no pain" and no score was higher than "mild pain". All babies were either "awake and alert" or "drowsy but easy to arouse" for the duration of the infusion, except for one who was difficult to arouse at the first assessment after returning to the ward. There was no clinical evidence of central nervous system toxicity in any baby.

The results for total bupivacaine plasma concentrations sampled from a peripheral vein are shown in table 2 and figure 1. Most concentrations were less than 2 μg ml$^{-1}$ but one baby had a concentration of 2.02 μg ml$^{-1}$ at 32 h. The same baby showed clear evidence of accumulation of bupivacaine throughout the extradural infusion.

We attempted to separate the free fraction of bupivacaine with a micro-partition system (Amicon) and measure its plasma concentration using HPLC. In most samples the volume of plasma obtained was insufficient for the separation method or the concentration of the free drug was below the sensitivity of the assay for the volumes of plasma available (approximately 0.1 μg ml$^{-1}$ for 100 μl).

*Table 2* Total plasma concentrations of bupivacaine associated with an extradural infusion sampled from a peripheral vein at different times. All assays used 100 μl of plasma

| Patient No. | Bupivacaine concentration (μg ml$^{-1}$) 4 h | 8 h | 16 h | 24 h | 32 h | 40 h |
|---|---|---|---|---|---|---|
| 1 | 0.21 | 0.36 | 0.78 | 1.26 | 0.81 | |
| 2 | 0.91 | | | | | |
| 3 | 0.96 | 0.96 | 0.55 | 0.60 | 0.79 | |
| 4 | 1.0 | 0.36 | 0.51 | 0.54 | 0.66 | |
| 5 | 1.0 | 0.8 | 0.67 | | | |
| 6 | 0.89 | 1.15 | 0.92 | 0.83 | | |
| 7 | 0.55 | 0.70 | 0.79 | 0.60 | 0.87 | 0.36 |
| 8 | 0.91 | 1.01 | 1.11 | 1.3 | 2.02 | |

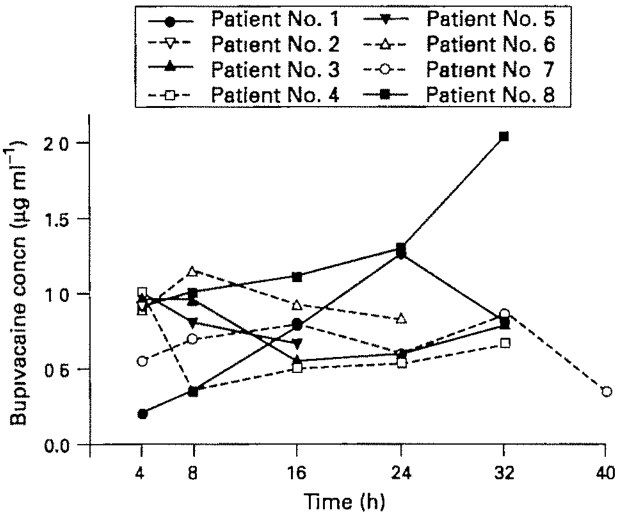

*Figure 1* Venous plasma concentrations of total bupivacaine during continuous extradural infusion, measured at 4, 8, 16, 24, 32 and 40 h

## Discussion

Extradural analgesia for postoperative pain control has become a more common technique in paediatric anaesthesia since the introduction of equipment specifically designed for use in babies and children.[3–6] Plasma concentrations of local anaesthetics during continuous extradural infusion have been measured in few children,[1 7 8] or babies.[8 9] Babies less than 6 months of age have an even greater potential for local anaesthetic toxicity than older children and adults because the free fraction of drug is increased.[10] The increased free fraction probably results from lower concentrations of binding proteins, principally $\alpha_1$-acid glycoprotein and albumin. The free fraction decreases inversely with age as the plasma concentration of $\alpha_1$-acid glycoprotein increases.

Berde reported from data collected from the members of the Society for Pediatric Anesthesia that seizures can occur in children at plasma concentrations of bupivacaine as low as 2 $\mu$g ml$^{-1}$.[1] Our study showed that some babies accumulate bupivacaine during continuous extradural infusion and can reach plasma concentrations in the range associated with local anaesthetic toxicity in children, despite infusion rates less than the maximum recommended by Berde.[1] This supports the findings of Wolf and colleagues[8] who showed that continuous extradural infusion of bupivacaine in the accepted dose can produce plasma concentrations within the toxic range in children, and Larsson, Olsson and Lönnqvist,[9] who found that babies accumulate bupivacaine during continuous infusions.

Wolf and colleagues measured plasma concentrations of bupivacaine associated with continuous lumbar or thoracic extradural infusions in 20 children aged 2 months to 4 yr.[8] After operation bupivacaine was infused at 0.25–0.375 mg kg$^{-1}$ h$^{-1}$ and additional boluses were given, with a maximum dose in any 4 h of 1.6 mg kg$^{-1}$. Two children, weighing 10 and 8.3 kg, had concentrations of 2.5 and 3.7 $\mu$g ml$^{-1}$, respectively, at 24 h. No toxic side effects were reported.

Larsson, Olsson and Lönnqvist[9] measured plasma concentrations of bupivacaine at 6 and 12 h in seven babies aged 0–7 months given a continuous extradural infusion.[9] They injected an initial dose of bupivacaine 1.5–1.9 mg kg$^{-1}$ with adrenaline and then infused bupivacaine 0.5–0.83 mg kg$^{-1}$ h$^{-1}$ without adrenaline. These doses are greater than the maximum recommended.[1] Larsson, Olsson and Lönnqvist[9] found a marked increase in plasma concentrations between 6 and 12 h, demonstrating accumulation of bupivacaine. The mean concentration at 6 h was 1.59 $\mu$g ml$^{-1}$ (range 1.2–2.1 $\mu$g ml$^{-1}$) compared with 2.06 (1.53–2.98) $\mu$g ml$^{-1}$ at 12 h. Two babies had central nervous system side effects, probably related to bupivacaine toxicity.

In conclusion, we have shown that babies can accumulate bupivacaine and achieve plasma concentrations above the threshold for toxic side effects, despite infusion rates below the currently accepted maximum. Although we can make no comment on the plasma concentration of unbound bupivacaine in our patients, babies have been shown to have a higher free fraction, at least to the age of 6 months, and a greater potential for toxic side effects. The size of our sample was small but we believe an extradural infusion rate of 0.375 mg kg$^{-1}$ h$^{-1}$ is probably an absolute maximum for babies younger than 12 months.

## Acknowledgements

We thank Anne Dye (Biochemistry Technician, Sir Humphry Davy Department of Anaesthesia, University of Bristol) for the assays of bupivacaine.

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# Analgesia after day-case knee arthroscopy: double-blind study of intra-articular tenoxicam, intra-articular bupivacaine and placebo

T. M. COOK, J. P. TUCKEY AND J. P. NOLAN

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## Summary

Arthroscopy of the knee is performed regularly on a day-case basis. Intra-articular bupivacaine produces transient analgesia and reports of analgesia using intra-articular morphine have produced conflicting results. Non-steroidal anti-inflammatory drugs given systemically can provide effective analgesia for this procedure. In this study we attempted to determine if intra-articular tenoxicam provided useful analgesia after day-case arthroscopy. Sixty three ASA I–II patients were allocated randomly to one of three groups to receive 40 ml of a solution containing 0.9% saline (group Pla), 0.25% bupivacaine (group Bup) or tenoxicam 20 mg (group Ten). The injection was made into the knee joint at the end of surgery, 10 min before tourniquet deflation. Verbal rating and visual analogue pain scores (at rest and on knee flexion), use of analgesia, mobilization and disturbance by pain at home were recorded for the next 48 h. There were no differences between pain scores in any of the three groups when tested at rest or on movement. Less analgesia was used in the first 24 h by patients in the tenoxicam group but the difference in time to first analgesia was not statistically significant. Side effects and disturbance by pain were similar in all groups. The use of intra-articular tenoxicam 20 mg at the end of arthroscopy reduced oral analgesic requirements during the first day after operation but did not alter patients' perception of pain. (*Br. J. Anaesth.* 1997; **78**: 163–168)

**Key words**
Pain, postoperative. Analgesics non-opioid, tenoxicam. Surgery, orthopaedic. Anaesthetics local, bupivacaine Non-steroidal anti-inflammatory drugs.

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Arthroscopy of the knee is associated with postoperative pain that may require systemic analgesia and can delay hospital discharge. It is common to undertake the procedure as a day case. Efforts have been made to determine the best method of pain relief, to maximize analgesia and minimize side effects. Analgesic approaches include systemic opioids or systemic non-steroidal anti-inflammatory drugs (NSAID).[1] The use of locally administered analgesia is appealing and intra-articular local anaesthetics[2 3] and more recently intra-articular opioids[4] have been reported to be effective.

In contrast with opioids, NSAID have principal effects peripherally and therefore local application to the site of injury should produce analgesia while minimizing systemic side effects.[5] We set out to determine if there is a role for intra-articular tenoxicam (Mobiflex) in the prevention of pain after knee arthroscopy.

## Patients and methods

Before starting the study the local Ethics Committee gave approval and the Medicines Control Agency provided an exemption to the product licence for tenoxicam. We studied 63 patients undergoing elective knee arthroscopy. All patients gave informed, written consent and were advised that the intra-articular use of the trial drugs was a non-licensed method of administration.

Patients receiving NSAID in the previous 7 days, who were allergic to NSAID or local anaesthetics, who had contraindications to NSAID or local anaesthetics, those who were or might be pregnant, those aged less than 16 yr or more than 75 yr and those known to have osteoarthritis of the knee were excluded. We also planned to exclude those patients found to have osteoarthritis at the time of surgery, although none was found.

Instruction was given on using a 100-mm visual analogue scale (VAS) with 0 mm labelled "no pain" and 100 mm "worst pain imaginable". Instruction was also given on completing a pain verbal rating scale (VRS): ratings were "no pain", "mild pain", "moderate pain" and "severe pain". Preoperative pain scores at rest and on movement were recorded.

No premedication was given. A standardized general anaesthetic was administered. A sleep dose of propofol and fentanyl 1 $\mu g\ kg^{-1}$ was followed by maintenance with isoflurane and 66% nitrous oxide in oxygen. Patients breathed spontaneously via a laryngeal mask airway and a circle breathing system. Monitoring included inspired oxygen, electrocardiograph, non-invasive arterial pressure, pulse oximetry and capnography.

Patients were allocated randomly (with sealed

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envelopes) to one of three groups. Group Bup received 0.25% bupivacaine 40 ml into the knee joint; group Ten received a 40-ml injection of 0.9% saline containing tenoxicam 20 mg; and group Pla received a placebo injection of 40 ml of 0.9% saline. These injections were administered into the knee joint, by the surgeon, 10 min before the limb tourniquet was deflated.

VAS and VRS scores were recorded 30, 60, 120 and 180 min after tourniquet deflation and on another five specified occasions over the first 48 h after surgery. All VAS and VRS scores were recorded "at rest" and "on movement" (knee flexion). Patients recorded their analgesic use over this time.

Additional analgesia was prescribed as co-proxamol (dextropropoxyphene hydrochloride 32.5 mg and paracetamol 325 mg) as required, up to eight tablets a day. A supply of co-proxamol was given to the patient to take home and patients were requested not to consume any other analgesics. Morphine 0.15 mg $kg^{-1}$ and co-proxamol were available on request while in hospital.

Age, weight, sex, preoperative pain scores, tourniquet times, surgical grade and surgical procedure were analysed (by one-way ANOVA and chi-square where appropriate) to exclude important differences between groups. Pain scores and analgesic requirements during the first 48 h were compared between groups using repeated measures ANOVA. The time to first analgesic use was studied by Kaplan–Meier survival analysis. Results were considered statistically significant when $P<0.05$. The statistical packages used were MS Excel (version 5.0) and SPSS for Windows (release 6.1) both running in MS Windows (release 3.1).

Previous studies suggested an SD of up to 20 mm for VAS scores after knee arthroscopy in patients receiving intra-articular analgesia.[6] With 20 patients in each group the study was designed to have 80% power to detect an 18-mm difference in VAS score at a 5% level of significance. We considered that differences of less than 18 mm would not be clinically significant.

## Results

Patient characteristics were similar in all groups with the exception that patients in group Bup were younger than those in the other groups. Indications

*Table 1* Patient data and surgical details (mean (SD or range) or number) *$P=0.013$ (ANOVA)

| | Group Pla ($n=21$) | Group Bup ($n=21$) | Group Ten ($n=21$) |
|---|---|---|---|
| Sex (M:F) | 19:2 | 17:4 | 15.6 |
| Age (yr) | 40.4 (23–61) | 28.6 (17–52)* | 39.6 (16–71) |
| Weight (kg) | 78.3 (39–103) | 74.8 (54–100) | 76.9 (63–101) |
| Indication for surgery ($n$) | | | |
| Pain | 14 | 18 | 10 |
| Unstable knee | 2 | 2 | 3 |
| Locking knee | 2 | 1 | 5 |
| Other/not stated | 3 | 0 | 3 |
| Procedure ($n$) | | | |
| Diagnostic arthroscopy | 3 | 7 | 10 |
| Debridement or biopsy | 4 | 4 | 1 |
| Partial meniscectomy | 14 | 10 | 10 |
| Tourniquet time (min) | 34.3 (10.6) | 27.2 (15.9) | 33.7 (20.9) |
| Grade of surgeon | | | |
| Consultant/senior registrar | 9 | 8 | 8 |
| Registrar | 12 | 13 | 13 |

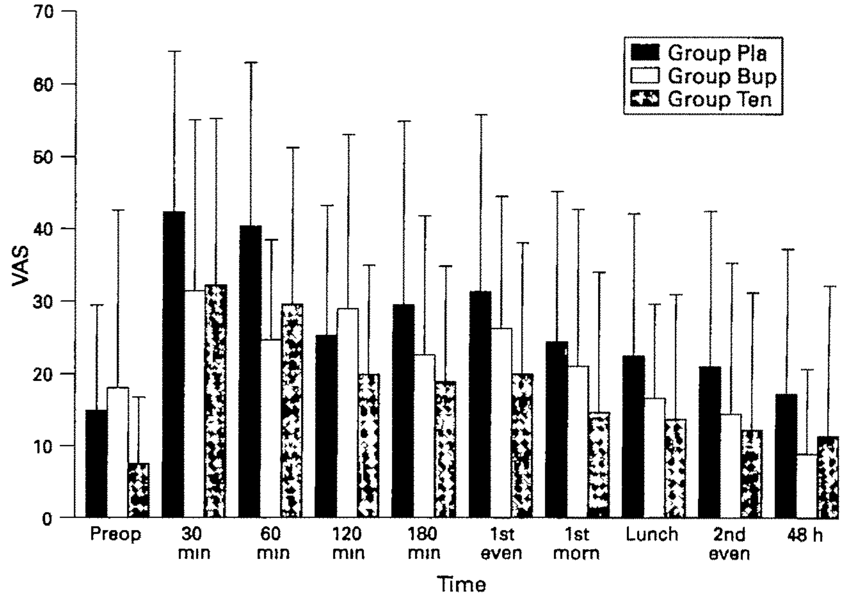

*Figure 1* Visual analogue scores (VAS) at rest (mean, SD).

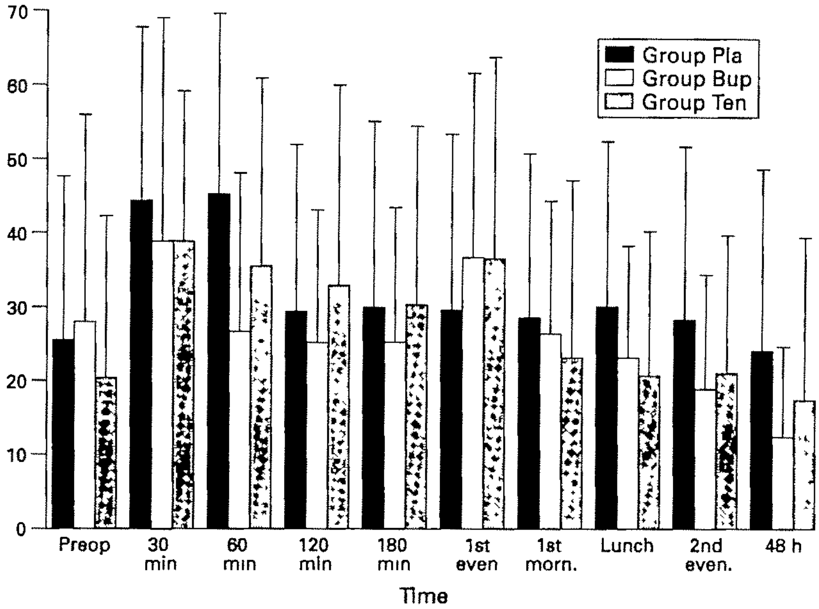

*Figure 2* Visual analogue scores (VAS) on movement (mean, SD).

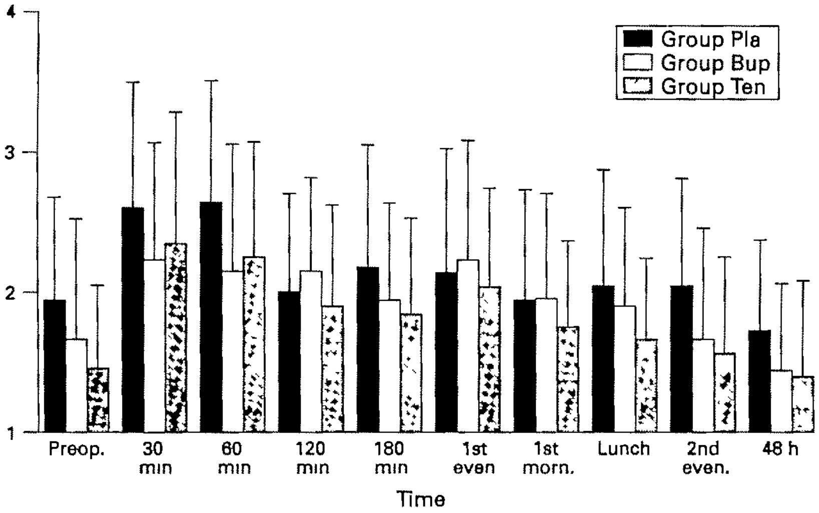

*Figure 3* Verbal rating scores (VRS) at rest (mean, SD).

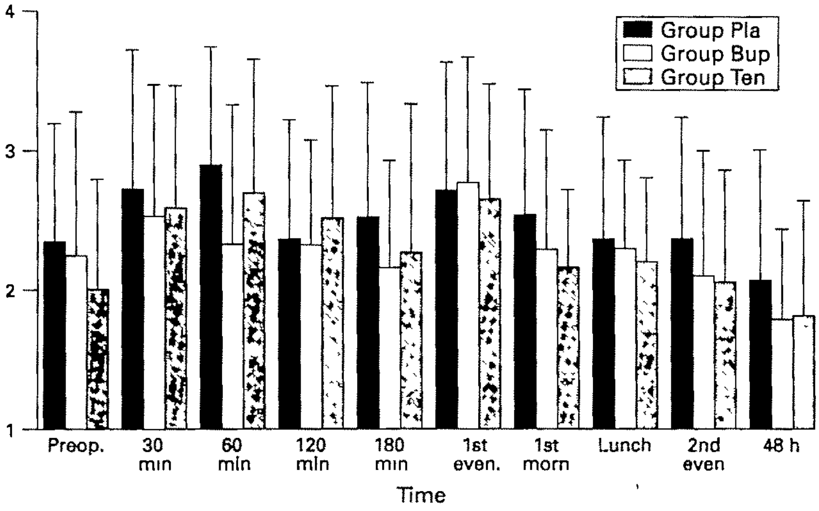

*Figure 4* Verbal rating scores (VRS) on movement (mean, SD).

*Table 2* Postoperative analgesic use (mean (95% confidence intervals)) *$P$=0.025 (ANOVA)

| | Group Pla ($n$=20) | Group Bup ($n$=21) | Group Ten ($n$=21) |
|---|---|---|---|
| Patients requiring morphine ($n$) | 3 | 3 | 3 |
| Time to first analgesia (min) | 107 (51–162) | 131 (63–198) | 213 (72–355) |
| Co-proxamol used in first 24 h ($n$) | 4.5 (3 1–5.9) | 4.4 (3.0–5.8) | 2.4* (1.6–3.3) |
| Co-proxamol used in first 48 h ($n$) | 6.0 (4.6–8.4) | 6.4 (4.2–8.6) | 4.1 (2.5–5.8) |

*Table 3* Mobilization and complication rates (mean (SD) or number)

| | Group Pla ($n$=20) | Group Bup ($n$=21) | Group Ten ($n$=21) |
|---|---|---|---|
| Time to walking (min) | 151 (66) | 188 (52) | 178 (80) |
| Patients admitted ($n$) (reason) | 1 (pain) | 1 (faint) | 1 (faint) |
| Nocturnal pain on first postoperative night ($n$) | 7 | 8 | 6 |
| Nocturnal pain on second postoperative night ($n$) | 7 | 4 | 5 |
| Excessive swelling ($n$) | 2 | 2 | 2 |
| Nausea or vomiting ($n$) | 1 | 0 | 4<br>(3 after morphine) |

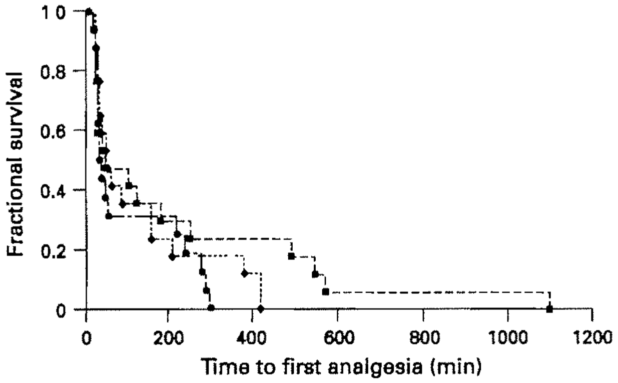

*Figure 5* Time to first analgesia. Survival analysis in the placebo (●), bupivacaine (◆) and tenoxicam (■) groups.

for surgery, distribution of diagnostic and interventional arthroscopy, duration of surgery and seniority of the surgeons did not differ significantly between groups (table 1). There were no significant differences in preoperative pain scores between groups. All patients completed the study. All questionnaires were returned but in some cases not all pain scores were completed.

There was no significant difference between groups in either VAS or VRS scores at any time, either at rest or during movement (figs 1–4).

The same number of patients (3) in each group received morphine. Time to first analgesia was longest in group Ten but the differences between groups was not significant and this was confirmed by survival analysis (fig. 5). All patients in group Pla requested analgesia within 6 h after surgery and in group Bup within 7 h. Four patients in group Ten required no analgesia for more than 8 h.

The number of co-proxamol tablets consumed in the first 24 h was significantly less in group Ten than in the other groups ($P$<0.05). The number of tablets taken in the first 48 h was less in group Ten than in the two other groups but this was not statistically significant (table 2). At home five patients took all the analgesia available to them in the first 48 h (16 tablets) while 10 patients took none.

There were no differences in the number of patients disturbed by pain on the first or second night after operation, or in reported adverse effects (table 3). All groups were similar in the time taken to mobilize. Mobilization was supervised by a physiotherapist who saw patients at least 2 h after operation. Most patients were mobile on the first attempt and 57 of the 60 patients were discharged during the same half-day. One patient from each group was admitted overnight (table 3).

## Discussion

Various factors have been implicated in pain after arthroscopy and the effectiveness of intra-articular analgesia. These include preoperative pain scores,[7] duration[7] and type of surgery,[8] seniority of surgeon,[7] use of general or regional analgesia,[3,9] volume injected,[3,10] addition of adrenaline[3] and timing of intra-articular injection relative to tourniquet deflation.[10] These findings are inconsistent and more importantly details have not been recorded or are poorly matched between studies. Not all studies were performed as day-cases,[11] premedication and peroperative opioid analgesia varied widely and in some studies suxamethonium was used.[3,9,11] Pain assessment varied, with few studies assessing pain on movement, and techniques of statistical analysis of pain scores differed. This makes the large number of studies difficult to compare. In the design of this study we attempted to use best practice in performance and analysis.

We included a placebo group in this study as the efficacy of intra-articular bupivacaine is not proved; we gave modest doses of fentanyl in the peroperative period for ethical reasons. Pain scores were assessed at rest and on movement and were comparable with those reported in most similar studies.

The availability of analgesia on demand may lead to a converging of pain scores, as differences in pain are translated into differences in behaviour and analgesic consumption. In this study differences between groups in measures of pain (VAS and VRS at rest, on movement and disturbance by pain at night) and behaviour (mobilization) were not statistically significant. The only statistically significant difference between groups was for analgesic use. Patients in group Ten used significantly less oral analgesia in the first 24 h than those in the two other groups. Time to first analgesia was twice as long in group Ten than in the other groups; this was not significant.

Some studies have found only small differences between analgesic requirements in intervention and placebo groups. In one study with no peroperative analgesia, 63% of patients in a placebo group required no analgesia in hospital and 29% used no analgesia at home.[12] The fact that some patients require negligible analgesia has led some to conclude that pain after arthroscopy is a poor model for testing efficacy of analgesics.[13] In this study 85% of our patients required analgesia at home and 25% were disturbed by pain on both of the first two nights after operation, while 15% took no analgesia at home. These findings do not suggest that pain after arthroscopy is insignificant but rather that it is variable.

Studies of intra-articular analgesia have revealed inconsistent findings, with local anaesthetics, particularly bupivacaine, found to be either ineffective[7] or effective only for short periods.[14] Intra-articular morphine has also been found to be ineffective,[3 6 10] to cause pain after injection[4] or to have a delayed onset of effect.[11 14] The combination of local anaesthetic and morphine has been found to provide rapid onset and prolonged analgesia[14] but also to be no more effective than morphine alone[10] or bupivacaine alone.[6]

NSAID are effective when given parenterally after arthroscopy[1] and may improve recovery.[15] The main site of action is peripheral, reducing nociception,[16] with fewer spinal effects.[5] NSAID may also reduce pain by modifying the local inflammatory process. As the pain of arthroscopy arises in the joint, it is logical to use a peripherally acting drug at the site of injury. One can postulate that using the drug locally may produce greater efficacy and reduced side effects. The difference in analgesia provided by matched doses of i.v. or intra-articular tenoxicam has not been determined and as this study had no i.v. group it did not test this hypothesis.

This study is the first blinded controlled examination of the use of an intra-articular NSAID for post-arthroscopy analgesia. The use of intra-articular ketorolac has been reported in three studies which claimed an analgesic effect equivalent to that of intra-articular local anaesthetic[17 18] and morphine.[19] These studies had no placebo group, used large doses (six times the current recommended parenteral dose) and in two studies pain scores were evaluated for only 2 h after operation. Diclofenac has also been used by the intra-articular route in an uncontrolled series of patients.[20] Good analgesia was reported but there have been reports of the injection causing both pain[19] and inflammation (personal communication, Ciba Pharmaceuticals).

Tenoxicam is an NSAID of the oxicam class with a prolonged elimination half-life.[21] It has a favourable side effect profile as it causes less gastrointestinal irritation than diclofenac SR, aspirin or indomethacin.[21] It has been used parenterally for knee arthroscopy[22] when it reduced pain in the first hour after operation. As the drug is water soluble and does not require a solubilizing agent, it is particularly suitable for intra-articular injection.

Several NSAID have effects on animal and human cartilage (reduced chondrocyte biosynthesis and cartilage destruction) *in vitro* and *in vivo* that can be deleterious,[23] particularly to patients with osteoarthritis. These effects vary between different NSAID.[24] In contrast with other NSAID, tenoxicam may not suppress chondro-formative processes in human osteoarthritic cartilage (*in vitro*)[25] and may have beneficial effects.[26] Further, tenoxicam tends to be concentrated in the synovium rather than the cartilage.[27] While there may be some question as to whether or not all NSAID are safe for intra-articular injection we believe tenoxicam is safe. Despite this, for safety reasons we excluded patients with osteoarthritis.

The prospect of using carefully selected NSAID intra-articularly raises the possibility of providing intra-articular "balanced analgesia". One study compared intra-articular ketorolac with intra-articular morphine and the combination of both.[18] Arthroscopies were performed under bupivacaine local anaesthesia with sedation. The conclusions were that each drug provided equivalent analgesia with no benefit from combining the two; there was no placebo group. It is not known if the anti-inflammatory effect of the NSAID interferes with peripheral opioid analgesia, which requires tissue inflammation for expression of peripheral opioid receptors.[3]

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*British Journal of Anaesthesia* 1997; 78: 169–171

# Brain tissue oxygenation in patients with cerebral occlusive disease and arteriovenous malformations

W. E. HOFFMAN, F. T. CHARBEL, G. EDELMAN AND J. I. AUSMAN

## Summary

It is not clear if ventilation with oxygen increases brain tissue oxygen pressure ($P_{O_2}$) during ischaemia. We have measured brain tissue $P_{O_2}$, carbon dioxide pressure ($P_{CO_2}$) and pH during baseline anaesthesia and oxygen ventilation in non-ischaemic control patients ($n$=9), patients with cerebral occlusive disease ($n$=11) and patients with arteriovenous malformations (AVM, $n$=12). The same anaesthetic treatment was given to all groups and anaesthesia was constant during the study. Arterial pressure, brain temperature and arterial blood-gas tensions were similar between groups. Under baseline conditions, brain tissue $P_{O_2}$ was mean 4.2 (SD 1.4) kPa in the controls and was 70% lower in patients with ischaemia and AVM. Patients with occlusive disease also had elevated tissue $P_{CO_2}$ and acidosis. During oxygen ventilation, $P_{O_2}$ increased to 7.5 (2.9) kPa in controls and this was 50% greater than the increase in the ischaemia and AVM patients. The results showed that baseline tissue oxygenation and increases in $P_{O_2}$ during hyperoxia were attenuated in patients with ischaemia or AVM. (*Br. J. Anaesth.* 1997; **78**: 169–171)

**Key words**
Brain, ischaemia. Brain, carbon dioxide. Complications, arteriovenous malformation. Carbon dioxide, partial pressure.

Under normal conditions, brain tissue $P_{O_2}$ is reported to be in the range 3.3–5.2 kPa in animals and patients.[1–3] Tissue oxygenation may be inhibited by cerebral occlusive disease or by arterial venous malformations (AVM), which attenuate cerebral perfusion pressure by producing a low resistance shunt for blood flow.[4–6] It has been reported that the upper limit of tissue oxygenation is controlled in normal brain tissue during oxygen ventilation, but that these regulating mechanisms are missing after head injury.[3] Little is known of tissue changes in $P_{O_2}$ during hyperoxia in tissue affected by occlusive disease or AVM. The purpose of this study was to evaluate the effect of oxygen ventilation in patients with cerebral occlusive disease and AVM compared with non-ischaemic controls.

## Patients and methods

The studies were approved by the University of Illinois Institutional Review Board for Clinical Research and informed consent was obtained. Patients in group 1 ($n$=9) served as controls for the study. None of these patients bled or had clinical signs of ischaemia before surgery. Neurosurgery was performed in these patients for clipping of cerebral aneurysms. Patients in group 2 ($n$=11) had evidence of cerebral ischaemia, as determined by neurological examination or the presence of transient ischaemic episodes. Decreased regional cerebral perfusion was confirmed in these patients by single photon emission computed tomography (SPECT) or cerebral angiography. Six of these patients were undergoing extracerebral to intracerebral vascular bypass, two patients cerebral aneurysm surgery with confirmed cerebral vasospasm and three patients had a cerebral embolism. Patients in group 3 ($n$=12) were undergoing neurosurgery for AVM resection. Nine of these patients had previous neuroradiological AVM embolization procedures performed before AVM resection.

All patients were anaesthetized with thiopentone 3–5 mg kg$^{-1}$ and fentanyl 10–15 μg kg$^{-1}$. Tracheal intubation was facilitated with vecuronium 0.1 mg kg$^{-1}$ and the lungs ventilated with 0.5–1.5% isoflurane and oxygen in room air (inspired oxygen fraction=0.4). Oesophageal temperature was measured and allowed to decrease to approximately 34°C. Arterial carbon dioxide tension ($Pa_{CO_2}$) was adjusted to 3.9–4.6 kPa. Monitoring included mean radial arterial pressure (MAP) measured by a Marquette Electronics Tramscope (Milwaukee, WI, USA); end-tidal isoflurane and $P_{CO_2}$ were measured with a Datex Ultima (Helsinki, Finland).

After craniotomy, a $P_{O_2}$, $P_{CO_2}$, pH and temperature sensor (Paratrend, Biomedical Sensors, Malvern, PA) was inserted into cortex tissue (diameter=0.5 mm). The sensor is a sterile, disposable device comprised of two modified optical fibres

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*Table 1* Mean arterial pressure (MAP), arterial oxygen and carbon dioxide partial pressures and pH, tissue carbon dioxide partial pressure, pH and brain temperature during 40% (baseline) and 100% oxygen ventilation (oxygen) in controls, and in those with cerebral occlusive disease (COD) and arteriovenous malformations (AVM) (mean SD)). $Pa_{\text{O}_2}$=arterial $P\text{O}_2$, $Pa_{\text{CO}_2}$=arterial $P\text{CO}_2$, $\text{pH}_a$=arterial pH, $Pt_{\text{CO}_2}$=tissue $P\text{CO}_2$, $\text{pH}_t$ = tissue pH *$P<0$ 05 compared with baseline, †$P<0.05$ compared with control

| Group | Treatment | *n* | MAP (mm Hg) | $Pa_{\text{O}_2}$ (kPa) | $Pa_{\text{CO}_2}$ (kPa) | $\text{pH}_a$ | $Pt_{\text{CO}_2}$ (kPa) | $\text{pH}_t$ | Brain temp (°C) |
|---|---|---|---|---|---|---|---|---|---|
| Control | Baseline | 9 | 86 (15) | 24.9 (7 3) | 4.3 (0.4) | 7.47 (0.04) | 6.4 (0.8) | 7.14 (0.15) | 35.6 (1.3) |
| | Oxygen | | 87 (15) | 54 0 (7 6)* | 4.3 (0.6) | 7.43 (0.07) | 6.3 (0.8) | 7.18 (0.10) | 35.6 (1.3) |
| COD | Baseline | 11 | 88 (12) | 29 2 (4.1) | 4.5 (0.4) | 7.42 (0.06) | 9.2 (4.9)† | 6.85 ( 0.25)† | 35.0 (0.6) |
| | Oxygen | | 88 (12) | 58.7 (3 3)* | 4.8 (0.3) | 7.38 (0.03) | 9.1 (3.7)† | 6.88 (0.25)† | 34.9 (0.6) |
| AVM | Baseline | 12 | 80 (8) | 23.3 (4.7) | 4.3 (0.7) | 7 43 (0 07) | 6.7 (1 2) | 7 09 (0.20) | 35.2 (0.9) |
| | Oxygen | | 81 (8) | 52.3 (8.4)* | 4.3 (0.5) | 7.44 (0.05) | 6.5 (1.2) | 7.17 (0.17) | 35.2 (0.9) |

for measurement of $P\text{CO}_2$ and pH, a miniaturized Clark electrode for $P\text{O}_2$ measurement and a thermocouple for measurement of temperature. The sensor was calibrated with three precision gases supplied with the monitor before insertion into the patient. The gases are: 1=2% carbon dioxide, 15% oxygen, balance nitrogen; 2=5% carbon dioxide, 15% oxygen, balance nitrogen; 3=10% carbon dioxide, 15% oxygen, balance nitrogen. The calibration range and 95% confidence limits for each sensor have been determined in *in vitro* testing: oxygen (range 0–15.7 kPa, 95% confidence limits +0.1 kPa); carbon dioxide (range 1.3–10.5 kPa, 95% confidence limits +0.4 kPa); pH (range 6.80–7.80, 95% confidence limits +0.03). The 0% to 90% response time for each sensor is: oxygen=70 s, carbon dioxide=143 s, pH=78 s.[7] All monitored variables were collected by computer using Labview (National Instruments, Austin, TX) every 10 s.

When the sensor was inserted, baseline tissue gas tensions, pH and temperature, MAP and blood-gas tensions were measured after a 30-min equilibration period. Inspired oxygen fraction was increased from 0.4 to 1.0 for 10 min and then returned to baseline levels. Samples for arterial blood-gas measurements were obtained under baseline conditions and during oxygen ventilation.

Data are reported as mean (SD). Differences in mean values between the three groups were analysed by analysis of variance with *post hoc* testing if a significant *F* value was found. Differences between baseline and oxygen administration were analysed using paired *t* tests. If data distribution failed the underlying assumptions for normality and equal variance, non-parametric analyses using Kruskal–Wallis or Wilcoxon tests were performed.

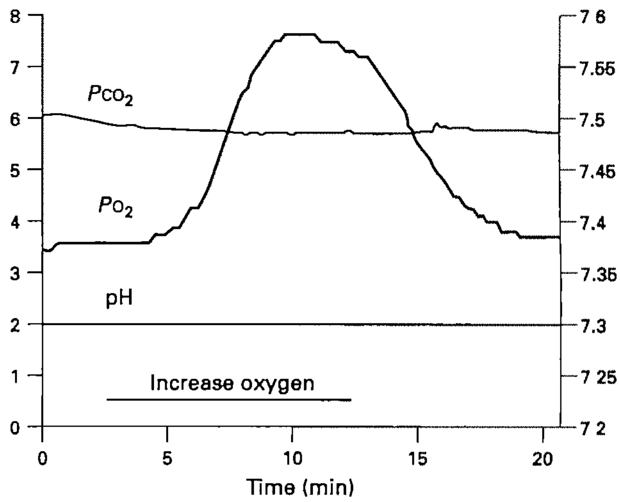

*Figure 1* Changes in $P\text{O}_2$, $P\text{CO}_2$ and pH during oxygen ventilation in a non-ischaemic patient. The scale for $P\text{O}_2$ and $P\text{CO}_2$ (kPa) is shown on the left and that for pH on the right. Oxygen ventilation produced an increase in $P\text{O}_2$ with no change in $P\text{CO}_2$ or pH.

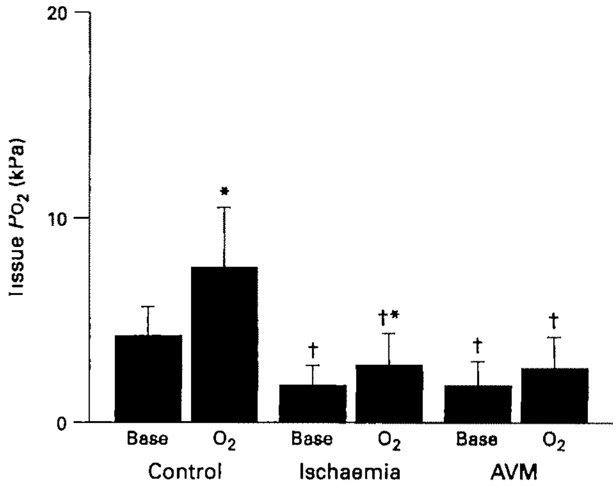

*Figure 2* Tissue $P\text{O}_2$ during baseline measurements (Base) and oxygen ventilation ($\text{O}_2$). Baseline $P\text{O}_2$ was greater in controls compared with those with cerebral occlusive disease and AVM. The increase in $P\text{O}_2$ during hypoxia was attenuated in cerebral occlusive disease and AVM compared with controls. *$P<0.05$ compared with baseline; †$P<0$ 05 compared with control.

## Results

Under baseline conditions, the physiological variables in table 1 were similar in control, ischaemic and AVM patients. With administration of 100% oxygen in the inspired gases, $Pa_{\text{O}_2}$ increased in all three groups to a similar degree. The response to oxygen ventilation in a normal patient is shown in figure 1. Tissue $P\text{O}_2$ increased in these patients during the increase in $Pa_{\text{O}_2}$ but there was no change in tissue $P\text{CO}_2$ or pH. Figure 2 show mean tissue $P\text{O}_2$ data for all patients. Under baseline conditions, tissue $P\text{O}_2$ decreased in ischaemic and AVM patients compared with controls, and the increase in $P\text{O}_2$ during oxygen administration was attenuated in ischaemic and AVM patients during hyperoxia. Tissue $P\text{CO}_2$ increased and pH decreased in ischaemic patients during the baseline period but neither variable changed during oxygen ventilation (table 1).

## Discussion

In non-ischaemic patients, we found a baseline tissue $P\mathrm{O_2}$ of 4.2 kPa. This is consistent with previous reports.[1–3, 8] During hyperoxia, tissue $P\mathrm{O_2}$ increased to 7.5 kPa in non-ischaemic patients. This agrees with the conclusions of Meixenberger and colleagues[3] that local mechanisms regulate the upper limit of tissue oxygenation. Tissue oxygenation decreased significantly in patients with cerebral occlusive disease and AVM under baseline conditions and during oxygen ventilation. This indicates that mechanisms which promote tissue oxygenation are attenuated in occlusive disease and AVM.

Previous studies have suggested that cerebral occlusive disease and AVM produce different types of ischaemia. Acute and chronic brain ischaemia during brain artery occlusion is associated with a decrease in $P\mathrm{O_2}$, an increase in $P\mathrm{CO_2}$ and acidosis.[1, 8–11] This is accompanied by loss of cerebrovascular reactivity to increases in $Pa_{\mathrm{CO_2}}$.[12] In contrast, with an AVM, cerebral tissue perfusion pressure and blood flow are decreased because of shunting of arterial blood flow away from normal tissue.[4–6, 13] Although AVM have been described as producing vascular paralysis and ischaemia,[14] studies have shown that carbon dioxide reactivity and pressure autoregulation are intact.[5, 6] In spite of the reported differences between these two types of ischaemia, we found that the tissue oxygenation response to oxygen ventilation was attenuated in both groups. This suggests that inadequate brain tissue oxygen delivery is a consistent problem in patients with cerebral occlusive disease and AVM.

In this study, patients with occlusive disease had significantly increased tissue $P\mathrm{CO_2}$ and decreased pH. This supports previous reports that carbon dioxide clearance is attenuated and metabolic acidosis may be present in these regions.[9, 11, 15, 16] In contrast, in tissue adjacent to an AVM, $P\mathrm{CO_2}$ and pH did not differ from control values, possibly because decreased tissue metabolism would lower carbon dioxide production and normalize pH in hypoxic tissue.[17] One concern is that the lack of change in brain tissue $P\mathrm{CO_2}$ and pH results from a lack of sensitivity of the sensors rather than absence of a tissue change. However, in previous studies we have shown that tissue $P\mathrm{CO_2}$ and pH change in patients during hypercapnic challenge.[9] This supports the fact that the lack of changes in tissue $P\mathrm{CO_2}$ and pH during increases in oxygen ventilation were accurate.

In summary, these results showed that brain tissue $P\mathrm{O_2}$ was lower in patients with cerebral occlusive disease and AVM compared with non-ischaemic patients. During oxygen ventilation, tissue $P\mathrm{O_2}$ increased (4.6 kPa) in control patients; this was significantly greater than the response in patients with occlusive disease and AVM. Simultaneous measurements of tissue $P\mathrm{CO_2}$ and pH indicated that the metabolic characteristics of occlusive disease and AVM were different but that inadequate tissue oxygenation was a consistent problem in both groups.

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# Blood loss during first trimester termination of pregnancy: comparison of two anaesthetic techniques

J. E. HALL, W. S. NG AND S. SMITH

## Summary

We have compared the effects of two anaesthetic techniques on blood loss during suction termination of pregnancy. Forty-eight ASA grade I-II patients were allocated randomly to one of two groups: group 1 received propofol induction followed by a standard propofol infusion; group 2 received propofol induction followed by maintenance with 1% isoflurane. Both groups received bolus doses of either propofol (group 1) or isoflurane (group 2) if anaesthesia was too light. All patients were given fentanyl 1 $\mu$g kg$^{-1}$ on induction. The products of conception were evacuated into a closed suction bottle. The products were diluted with 500 ml of heparinized saline, filtered and left for 20 min. Estimation of blood loss was performed by atomic absorption spectrometry. Mean blood losses were 40.4 ml for the isoflurane group and 18.8 ml for the propofol group. This difference was statistically significant ($P$=0.0011), although actual volumes of blood loss were small and not clinically significant. (*Br. J. Anaesth.* 1997; **78**: 172–174)

**Key words**
Anaesthetics i.v., propofol. Anaesthetics volatile, isoflurane. Blood, loss. Surgery, gynaecological.

Suction termination of pregnancy is performed frequently, although the number of suction terminations has decreased recently as medical termination becomes more common. The operation is generally regarded as safe, although severe uterine haemorrhage may occur.

Volatile anaesthetic agents are often avoided during suction termination of pregnancy. Halothane, enflurane and isoflurane are known to depress the activity of the human myometrium leading to increased blood loss.[1] Because of the effect of volatile agents on the pregnant uterus, some anaesthetists prefer to use either intermittent bolus doses of propofol or propofol infusion, although on an empirical basis, as no study has investigated the effect of propofol on blood loss in the first trimester uterus.

## Patients and methods

The study was approved by the local research Ethics Committee. We studied 48 patients undergoing suction termination of pregnancy as a day-case procedure after obtaining written informed consent. All subjects were ASA I or II with a fetal gestational age of 9–12 weeks. Gestational age was determined clinically by dates and by bimanual examination. Patients were excluded before operation if the standard anaesthetic technique could not be followed. These factors included the patient having a known allergy to any of the anaesthetic agents and when body mass index was 50% greater than normal.

On the morning of operation, the patient's haemoglobin concentration was measured. All patients received a gemeprost 1 mg vaginal pessary at least 1.5 h before operation. Patients were excluded if any external blood loss was seen before operation. No premedication was given. Patients were allocated randomly to one of two groups to receive the following anaesthetics: group 1, after preoxygenation, patients received fentanyl 1 $\mu$g kg$^{-1}$ followed by an induction dose of propofol (2–3 mg kg$^{-1}$). A propofol infusion was started using a standard regimen of 12 mg kg$^{-1}$ h$^{-1}$ for 10 min, and then 9 mg kg$^{-1}$ h$^{-1}$ for 10 min. If anaesthesia was deemed to be light, it was supplemented with bolus doses of propofol (20 mg). Patients breathed 66% nitrous oxide in oxygen via a face mask; group 2, after preoxygenation, patients received fentanyl 1 $\mu$g kg$^{-1}$, followed by an induction dose of propofol (2–3 mg kg$^{-1}$). Anaesthesia was maintained with 1% isoflurane (measured concentration) and 66% nitrous oxide in oxygen via a face mask. If anaesthesia was deemed to be too light, isoflurane concentration was increased by 0.5%, and a further 0.5% if necessary, reverting to a concentration of 1% isoflurane when the patient had stabilized.

In the operating theatre, a screen separated the surgeon and anaesthetist. The time of the start of anaesthesia was noted, as was the time when dilatation of the cervix commenced. Oxytocin 10 u. was administered i.v. when the cervix was dilated. All terminations were performed by suction curettage

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and uterine contents were aspirated into a closed system suction bottle. The surgeon assessed the quality of uterine contraction by bimanual examination and the operation was not considered complete until the surgeon was satisfied. Surgical and anaesthetic times were noted. Surgical time was the time between commencement of dilatation of the os and end of operation. Anaesthetic time was the time between giving the induction agent and discontinuation of nitrous oxide at the end of the procedure. Surgery and anaesthesia were performed by doctors graded senior SHO and above.

When the procedure was complete, the suction tubing was washed with 500 ml of heparinized normal saline. The contents of the suction bottle were then strained through a fine muslin mesh and left to drain for 20 min. The final sample of fluid was analysed for iron content by flame atomic absorption spectroscopy (FAAS).[2] Blood loss was calculated using the patient's haemoglobin concentration and iron content of the operative suction sample.

The results were analysed using a Minitab 2 sample Student's *t* test which does not rely on equality of variants. The results were considered significant when $P<0.05$.

## Results

We recruited 48 patients; four were withdrawn after consent had been gained: one because she received i.m. pethidine shortly before coming to the operating theatre, two patients had external blood loss after the gemeprost pessary was inserted and one was found to have an empty uterus on examination in theatre. Patient groups were similar in age, gestation of pregnancy, and surgical and anaesthetic times (table 1).

There was a highly significant difference between the two groups for blood loss (table 2).

*Table 1* Patient details (mean (SD or range))

| | Group 1—isoflurane ($n=23$) | Group 2—propofol ($n=21$) |
|---|---|---|
| Age (yr) | 22 (18–33) | 23 (18–35) |
| Gestation (weeks) | 10.3 (1.1) | 10.8 (1.1) |
| Surgical time (min) | 4.1 (1.7) | 3.6 (1.3) |
| Anaesthetic time (min) | 9.6 (2.5) | 9.5 (2.5) |

*Table 2* Measured blood loss in the two groups Significant difference $^{**}P=0.0011$ (Student's *t* test)

| | Group 1—isoflurane ($n=23$) | Group 2—propofol ($n=21$) |
|---|---|---|
| Blood loss (ml) | | |
| Range | 6–111 | 6–53 |
| Mean (SD) | 40.4 (26.1)** | 18.8 (11.8) |

## Discussion

Many studies have compared the effects of volatile and i.v. anaesthetic agents on uterine blood loss during termination of pregnancy. Halothane has been shown to cause increased blood loss during this procedure, although the results are not unequivocal. One large study[3] concluded that halothane led to increased blood loss, but the 87 patients studied were allocated to one of eight groups making each rather small. In addition, duration of anaesthesia was up to 35 min, which is prolonged by current standards. Increased blood loss was also shown with halothane in a comparison between halothane and alfentanil-supplemented anaesthesia.[4] Batt concluded that halothane was safe in spontaneous abortion,[5] in a large, although retrospective, 5-yr study. West and colleagues found that halothane did not differ from methohexitone and Althesin-supplemented anaesthesia.[6]

A study using enflurane[7] showed significantly increased blood loss compared with fentanyl-supplemented anaesthesia, but in this study high concentrations of enflurane (3%) were used and these would probably be avoided in current practice. There has been little work on newer agents, although Dolan, Eger and Margolis[8] in a small study concluded that isoflurane was in the same category as halothane in increasing blood loss during suction termination. This conclusion was based on a comparison with an earlier study.[3]

As Grant pointed out in an editorial,[9] this type of study suffers from the difficulties of measuring low blood loss. Commonly used techniques include measurement of volume collected by closed suction and colorimetric methods. It was felt that iron estimation by atomic absorption spectrometry might produce accurate results (see appendix). In fact, the measured blood loss in this study was similar to that in a recent study examining the use of oxytocin in suction termination of pregnancy, where colorimetric estimation was used.[10]

Our study attempted to mirror normal practice, using low concentrations of isoflurane, an i.v. induction agent and relatively brief surgical and anaesthetic times. In spite of these precautions there was still a statistically significant increase in blood loss with isoflurane. Admittedly, the anaesthetists and surgeons participating were not standardized, but all were experienced in the techniques required, the anaesthetic technique was accurately prescribed and all operations used suction curettage.

Total blood loss was low in both groups and the difference may not be clinically significant. The difference in blood loss could have more clinical relevance when general anaesthesia is given for planned terminations of a high gestational age or for evacuation of retained products of conception after incomplete spontaneous abortion. The latter operation is performed frequently between the eighth and 14th weeks of gestation and can be associated with considerable blood loss. This study suggests that the choice of anaesthetic technique could influence the degree of haemorrhage. In addition, if the differences in blood loss could be extrapolated from the first to the third trimester, there may be implications for haemorrhage during Caesarean section under general anaesthesia.

## Appendix

FAAS uses the principle that ground state atoms absorb electromagnetic radiation in a series of very narrow, well defined wavelengths, making the test very specific and sensitive. Iron is excited thermally and as it returns to its ground state it emits radiation of a characteristic wavelength The intensity of the radiation is directly proportional to the concentration of iron present. Blood loss was calculated using the patient's haemoglobin concentration and the iron content of the operative suction sample:

Haemoglobin molecular weight=64 458.

Haemoglobin contains four atoms of iron, that is 4×molecular weight of iron 55.85=223.7.

Therefore 1 g of haemoglobin contains (223 7/64 458) ×1000=3.47 mg Fe.

Haemoglobin lost by patient=
concentration of haemoglobin in sample×total volume of diluted sample.

$$\text{Blood loss by patient} = \frac{\text{Haemoglobin lost by patient}}{\text{Patient's haemoglobin concentration}}$$

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# Use of heparinase modified thrombelastography in liver transplantation

S. A. HARDING, S. V. MALLETT, T. D. PEACHEY AND D. J. COX

## Summary

Severe coagulopathies can occur during liver transplantation, particularly after reperfusion of the grafted liver. Heparin release has been proposed as one of the factors contributing to this coagulopathy. We have analysed the thrombelastograph (TEG) traces of 55 patients after reperfusion using native and heparinase-treated samples. In almost all cases an abnormal native TEG was improved *in vitro* by heparinase, demonstrating the presence of heparin or a heparin-like substance. The heparinase-modified TEG allowed assessment of the underlying coagulation status, providing a rational guide to blood component replacement or treatment of fibrinolysis. (*Br. J. Anaesth.* 1997; **78**: 175–179)

**Key words**
Liver, transplantation. Measurement techniques, thrombelastography. Blood, anticoagulants, heparin.

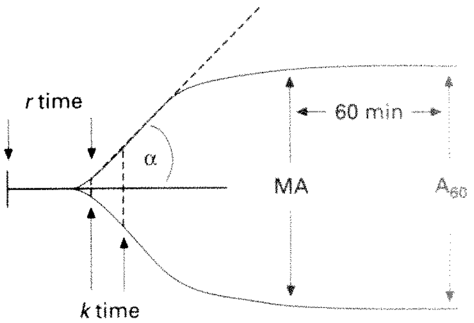

*Figure 1* Normal thrombelastographic trace. Normal range (plastic cup): $r$=21–30 mm, $k$=5–7 min, MA=45–54 mm and $\alpha$=30–40°.

Liver transplantation is frequently complicated by severe coagulopathies, particularly after reperfusion of the grafted liver. The cause of the marked deterioration in coagulation that accompanies reperfusion is incompletely understood but many potential factors have been implicated, including hyperfibrinolysis, DIC, platelet activation, trapping of platelets in the graft and a heparin-like effect.[1]

The thrombelastograph (TEG) has been shown to be a useful monitor of coagulation during liver transplantation and provides a rational approach to the use of blood component therapy or pharmacological intervention.[2] A normal TEG is shown in figure 1. Characteristic changes in the TEG trace occur after reperfusion of the grafted liver and have been described by several authors.[2–4] There is prolongation of the reaction time ($r$) and coagulation time ($r+k$), and a decrease in maximum amplitude (MA) and clot formation rate ($\alpha$). In our experience, the first TEG after reperfusion ($r$+10 min) frequently shows a straight line (no trace), demonstrating no clot formation during the 60 min that the sample is running. Several factors are thought to be responsible for this coagulopathy, including heparin release from the implanted liver graft. There have been several reports that document the presence of heparin-like activity immediately after reperfusion. The frequency of this heparin effect is reported to be between 25% and 95% of cases.[5 6]

Kang and colleagues have suggested that where there is demonstrated correction of the reaction time in blood treated with protamine sulphate *in vitro*, administration of protamine 50 mg can be used to antagonize the heparin effect *in vivo*.[1] Two cases have been reported where a coagulopathy developing 30 min after graft reperfusion was reversed clinically by protamine sulphate 50 mg, resulting in cessation of oozing from cut surfaces and normalization of the TEG.[7] Using protamine titration *in vitro*, Bakker and colleagues demonstrated a heparin effect in all of 15 recipients where heparin had been administered to the donor before removal of the liver graft and in one of five recipients whose donor had not been heparinized.[8] This suggests that heparin may bind to the endothelium during the donor procedure and subsequently be released into the circulation on reperfusion. It is standard practice in the UK to administer heparin 300 u. $kg^{-1}$ to all donors before organ harvesting. There may also be an additional component of endogenously derived heparin-like substance released by the donor liver from hepatic vascular endothelium damaged during ischaemia or reperfusion.

Heparinase is an enzyme obtained from *Flavobacterium heparinum* which specifically cleaves the polysaccharide portion of the anticoagulant

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proteoglycans heparin and heparan sulphate. Dietrich, Silva and Michelacci demonstrated that heparinase catalyses an eliminase reaction directly within the antithrombin III binding site of heparin[9] making it a potent reagent for eliminating the anticoagulant effect of heparin. Heparinase has been shown to reverse the TEG effects of heparin and studies on normal volunteers have demonstrated that heparinase does not affect TEG variables of whole blood not containing heparin.[10] Protamine antagonizes the effects of heparin but may adversely affect coagulation if the dose of protamine is not matched to the quantity of heparin in the sample.[11]

We have shown previously that the hypocoagulable state demonstrated on the TEG is largely reversed by administration of heparinase *in vitro*.[12] Since 1994 we have been using heparinase-coated sample pots (Heparinase I, 2 u.; Haemoscope Corp) in the TEG run simultaneously with the native sample after reperfusion. Where an abnormal TEG is improved by heparinase, this demonstrates the presence of heparin or heparan sulphate. In this study, we analysed the TEG tracings of 55 patients undergoing liver transplantation.

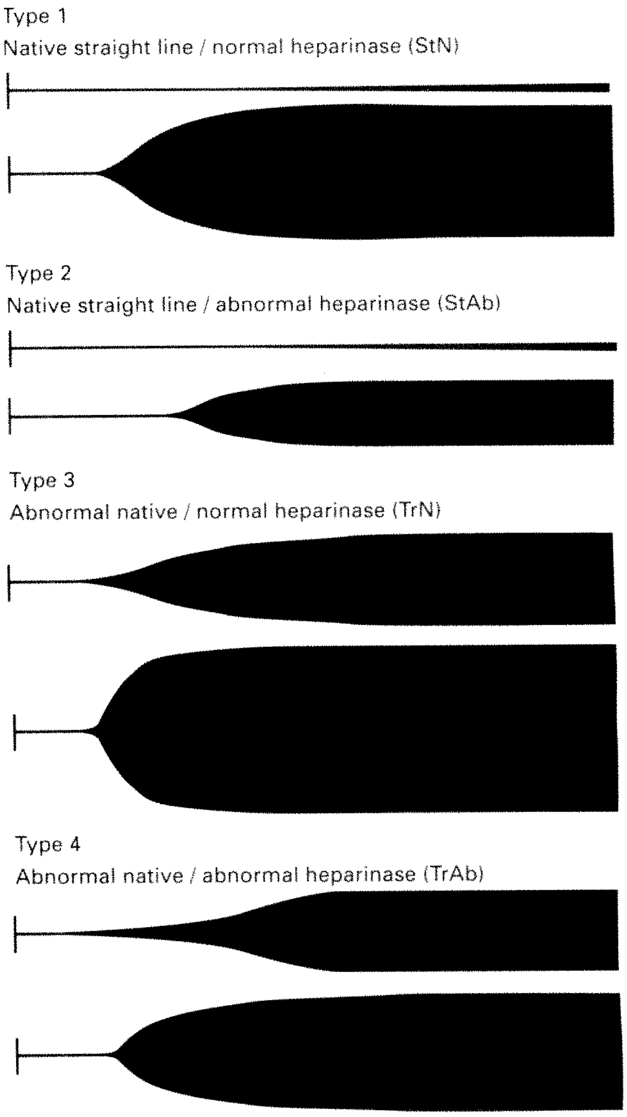
Type 1
Native straight line / normal heparinase (StN)
Type 2
Native straight line / abnormal heparinase (StAb)
Type 3
Abnormal native / normal heparinase (TrN)
Type 4
Abnormal native / abnormal heparinase (TrAb)

*Figure 2* Examples of thrombelastographic traces at reperfusion.

## Patients and methods

We examined the TEG tracings of 55 consecutive patients undergoing liver transplantation. Patients undergoing liver transplantation for fulminant hepatic failure were excluded. The diagnosis and Child's classification of the patients studied are given in table 1. Miscellaneous diagnoses were Wilson's disease (1), glycogen storage disease (1) and chronic active hepatitis (3). All blood samples for TEG analysis were obtained from a non-heparinized arterial cannula. Paired TEG traces were run simultaneously for all samples obtained after reperfusion. One sample had nothing added to it (native blood) and the other sample was treated with heparinase.

Patients were classified into four groups, according to the appearance of the TEG tracing at reperfusion + 10 min (R+10) (fig. 2). The native TEG sample was placed into one of two groups: a straight line (no trace) at 60 min or an interpretable trace within 60 min. The corresponding heparinase traces were also allocated to one of two groups: normal or abnormal, as defined by TEG variables. For the purposes of this study an abnormal trace was considered to be a coagulation time in excess of 60 mm of trace or a maximum amplitude of less than 35 mm, these being the values which we consider to require treatment with blood components at this stage of operation.

Total transfusion of blood and blood components were recorded for all three stages of the procedure. Red blood cells were transfused to maintain packed cell volume at 27–30%. Blood component therapy was administered on the basis of TEG criteria and the presence or absence of bleeding from surgical sites.

*Table 1* Diagnostic category and Child's classification

| | Child's A | Child's B | Child's C |
|---|---|---|---|
| Cirrhosis | 5 | 16 | 14 |
| PBC/PSC | 1 | 8 | 3 |
| Re-transplant | 0 | 1 | 2 |
| Miscellaneous | 1 | 2 | 2 |

Statistical analysis of blood transfusion requirements after reperfusion (unclamping of portal venous clamp and reperfusion of the liver to end of surgery) was carried out using the Kruskal–Wallis test with adjustment for ties. The Mann–Whitney *U* test was applied to individual groups.

Protamine 1 mg kg$^{-1}$ was given if a heparin effect was demonstrated on the TEG and there was clinical evidence of non-surgical bleeding caused by coagulopathy. Aprotinin (2 million kiu loading dose at the start of the procedure, followed by infusion of 500 000 kiu h$^{-1}$) was used according to our institutional criteria (patients with hepatic cirrhosis and those with markedly abnormal preoperative coagulation studies).

## Results

Analysis of the R + 10 TEG traces revealed only four of 55 traces which were unchanged by heparinase

*Table 2* TEG findings at reperfusion+10 min

| Native TEG | Heparinase TEG: normal trace | Heparinase TEG: abnormal trace |
|---|---|---|
| Straight line ($n$=39) | 18 | 21 |
| Interpretable trace ($n$=16) | 11 | 5 |

*Table 3* TEG groups: reperfusion+10 min. Stage III (after reperfusion) blood transfusion (mean (SEM) [range])

| TEG | $n$ | Received aprotinin | Received protamine | Blood transfusion (u.) |
|---|---|---|---|---|
| StN | 18 | 14 | 7 | 1.56 (0.63) [0-9] |
| StAb | 21 | 18 | 9 | 4.48 (1.26) [0-25] |
| TrN | 11 | 6 | 4 | 1.64 (0.43) [0-4] |
| TrAb | 5 | 4 | 2 | 1.40 (0.68) [0-3] |

(tables 2, 3); 39 of the native samples had a straight line TEG, of which all but one were improved by heparinase. The remaining patient had a straight line TEG which was unchanged by heparinase. This particular patient, who had received aprotinin, developed a severe coagulopathy after reperfusion which was not improved by infusion of FFP, cryoprecipitate and platelets, or administration of protamine. She died several hours after operation with intractable coagulopathy and circulatory collapse.

Sixteen patients had an interpretable trace at reperfusion; 13 of these were improved by heparinase. The three patients whose TEG was unchanged by heparinase at R+10 min developed prolongation of coagulation time in the native sample at R+30 min and demonstrated a heparin effect at that time. Where the native sample was a straight line, the heparinase sample revealed a normal TEG in 18 (46%) patients. Where the native sample was an interpretable trace, the heparinase trace was normal in 11 (69%) patients.

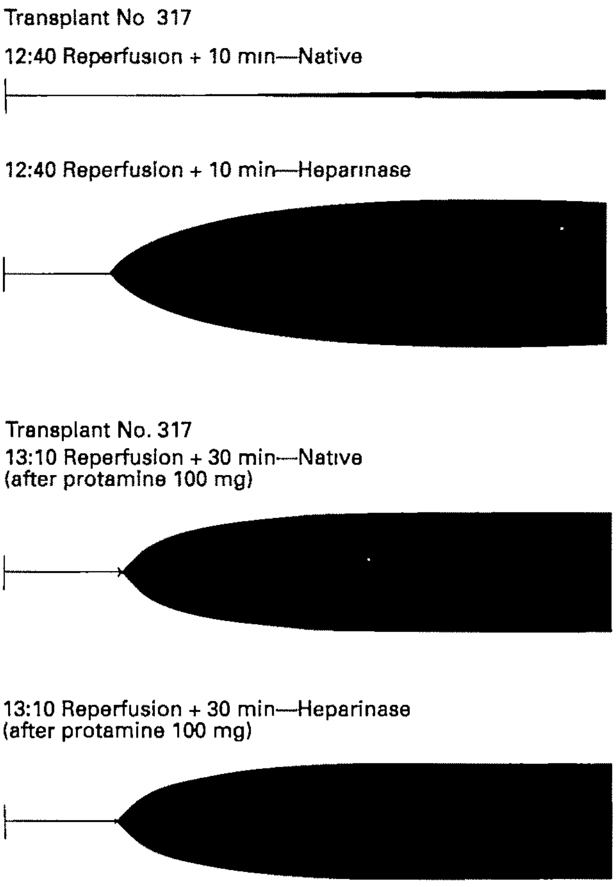

*Figure 3* Example of heparin effect reversed by protamine.

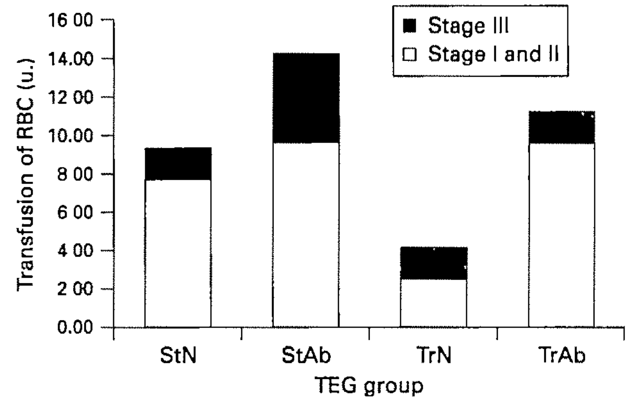

*Figure 4* Mean blood transfusion StN=Straight line native trace, normal underlying coagulation ($n$=18). Median transfusion stage III: 0 u of red blood cells (RBC) (range 0–9 u.), StAb=straight line native trace, abnormal underlying coagulation ($n$=21). Median transfusion stage III: 3 u. of RBC (range 0–25 u.); TrN=interpretable native trace, normal underlying coagulation ($n$=11). Median transfusion stage III: 1 u. of RBC (range 0–4 u.); TrAb=interpretable native trace, abnormal underlying coagulation. ($n$=5). Median transfusion stage III: 1 u. of RBC (range 0–3 u.) In stages I and II (dissection and anhepatic stage) blood loss (and therefore RBC transfusion) is generally related to surgical factors and the presence of portal hypertension, and is therefore presented separately to stage III (after reperfusion) blood loss which is more usually related to coagulopathy.

Protamine was administered in 26 cases. In cases where protamine was not administered, the heparin effect lasted 60–200 min. One patient who had received protamine developed recurrence of the heparin effect immediately after operation and received a second dose. In all cases where protamine was administered, correction of the TEG changes occurred (fig. 3).

Aprotinin was administered in 42 cases. In three of the 13 patients who did not receive aprotinin, the TEG after reperfusion was a straight line but the heparinase TEG revealed significant fibrinolysis which was treated with an i.v. bolus of tranexamic acid 500 mg. None of the patients who received aprotinin developed evidence of fibrinolysis on the TEG.

Mean blood transfusion for the four groups of patients is shown in figure 4. Statistical analysis of stage III (after reperfusion) transfusions revealed that patients who exhibited both a straight line native TEG and abnormal coagulation on the heparinase-modified trace (St Ab) had significantly higher transfusion requirements at this stage than any other group ($P$=0.01). There was no significant difference in stage III red blood cell (RBC) transfusion between patients who had an interpretable trace (irrespective of whether or not the heparinase-modified TEG was normal) and those patients who had a straight line TEG at reperfusion but had normal underlying coagulation ($P$=0.99).

Mean core temperature of the patients was 36.4 °C and at no time did any patient have a central temperature less than 35 °C.

## Discussion

The use of heparinase-modified TEG demonstrated the presence of heparin or a heparin-like substance after reperfusion of the grafted liver in all but one of the 55 patients studied. This "heparin effect" was variable both in magnitude and duration. The clinical significance of this heparin effect is uncertain as in many cases it is self-limiting and requires no specific treatment, however, in some patients it undoubtedly contributes to reperfusion bleeding. A "straight line" TEG in patients with good underlying coagulation rarely results in obvious bleeding at the wound site. There was no significant difference in stage III transfusion requirements between patients with good underlying coagulation irrespective of whether or not a marked heparin effect was demonstrated.

Our results indicate that patients who have an underlying coagulopathy are most sensitive to this effect. Transfusion requirements after reperfusion were significantly greater in patients who had both a "straight line" native TEG and abnormal underlying coagulation. In the absence of a heparin effect, poor coagulation treated according to conventional criteria did not result in significantly greater blood loss after reperfusion, but the numbers of patients in this particular group were insufficient to draw definitive conclusions.

It is possible that some liver transplant recipients may have a greatly increased sensitivity to heparin at reperfusion because of a combination of underlying coagulopathy and reduced heparin clearance. Clearance of heparin and heparan sulphate is known to be significantly prolonged in patients with liver disease[13] and it is possible that until the grafted liver achieves adequate function, that this is also the case in transplant recipients.

The origin of this heparin effect remains open to speculation but there is evidence for both exogenous and endogenous sources. All our donors had received heparin 300 u. kg$^{-1}$ according to standard UK practice. It is likely that this exogenously administered heparin contributes to this phenomenon,[14] even though the donor liver is flushed routinely with 4.5% albumin 500 ml before completion of the venous anastomoses. It is unclear if there is a significant component caused by endogenous heparan sulphate released from the damaged vascular endothelium of the ischaemic liver graft. Increased plasma concentrations of thrombomodulin are a marker of endothelial cell damage[15] and a sudden marked increase in concentrations have been demonstrated in liver transplant recipients within 5 min of reperfusion.[16] It has been shown that even in circumstances where the donor received no heparin, heparin-like activity, as demonstrated by protamine titration, may be present after reperfusion of the grafted liver.[8]

McKee and colleagues demonstrated increased concentrations of heparan sulphate in cirrhotic patients who bled from varices compared with matched controls who did not bleed but were unable to demonstrate a correlation with any other coagulation profile in the two groups. They concluded that the presence of this anticoagulant may have an important role in determining bleeding risk.[13] It is possible that heparan released into the systemic circulation from the ischaemic hepatic vascular endothelium at reperfusion similarly results in increased bleeding in patients who are excessively sensitive to its presence by virtue of poor underlying coagulation.

Where a marked heparin effect is demonstrated and the patient has clinical evidence of abnormal bleeding because of coagulopathy, administration of protamine sulphate 50–100 mg is of value. Correction of clotting factor and platelet deficiency should be undertaken simultaneously according to institutional procedures.

In conclusion, the presence of heparin or a heparin-like substance is demonstrable on the TEG in virtually all liver transplant recipients after reperfusion of the graft. This effect is so consistent, although variable in magnitude, that it most likely represents an inevitable accompaniment to reperfusion. Provided graft function is adequate, it is generally not a significant cause of bleeding after reperfusion and corrects spontaneously within 1–2 h. However, some patients may be excessively sensitive to these trace amounts of heparin or heparan and where a heparin effect is demonstrated and the patient has clinical evidence of abnormal bleeding caused by coagulopathy, protamine sulphate 1 mg kg$^{-1}$ should be administered. Neutralase (Heparinase 1) has recently been used successfully in human studies to reverse the effects of heparin[17] and may prove to be a preferable alternative to protamine as it lacks the potentially serious side effects of anaphylaxis and pulmonary vasoconstriction.

In our series, the native TEG trace after reperfusion was rendered uninterpretable in more than 50% of patients because of the presence of a marked heparin effect. Conventional criteria for administration of blood products based on the assessment of the native TEG at this stage could result in unnecessary or excessive treatment with blood component therapy. Use of the heparinase-modified TEG allows rapid assessment of the contribution of heparin to coagulopathy after reperfusion. In addition, the underlying coagulation profile is revealed, thereby facilitating the diagnosis of fibrinolysis, clotting factor or platelet deficiency and enabling appropriate therapy to be instituted.

The use of heparinase-modified TEG to monitor coagulation during liver transplantation provides useful additional information over native TEG alone and we would recommend its routine practice in this group of patients.

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# Relationship between calculated blood concentration of propofol and electrophysiological variables during emergence from anaesthesia: comparison of bispectral index, spectral edge frequency, median frequency and auditory evoked potential index

M. Doi, R. J. Gajraj, H. Mantzaridis and G. N. C. Kenny

## Summary

We studied four electrophysiological variables (bispectral index (BIS), 95% spectral edge frequency (SEF), median frequency (MF) and auditory evoked potential index (AEP index)) in 10 patients during emergence from anaesthesia. We compared correlation of the signals with gradually decreasing calculated blood propofol concentrations, and evaluated the signal differences between preinduction and emergence from anaesthesia. Values of BIS, MF and SEF correlated with calculated blood concentrations of propofol during emergence from anaesthesia. The correlation was best with BIS, but was poor with MF and SEF at low calculated blood propofol concentrations. Although AEP index values did not correlate with calculated blood concentrations of propofol during emergence from anaesthesia, values after eye opening and before anaesthesia were well distinguished from those during emergence from anaesthesia. BIS correlated best with calculated blood concentrations of propofol. AEP index appeared to distinguish the awake from asleep state. (*Br. J. Anaesth.* 1997; **78**: 180–184)

**Key words**

Brain, evoked potentials. Monitoring, evoked potentials. Anaesthetics i.v., propofol. Anaesthesia, depth.

The major requirement of a monitor of anaesthetic depth is to distinguish consciousness from unconsciousness. Another desirable feature would be for the signal to provide an estimate of the effect of a given brain concentration of an anaesthetic agent to predict movement or awareness. Several processed EEG variables have been studied for use as a monitor of anaesthetic depth, including bispectral index,[1-3] median frequency[4,5] and 95% spectral edge frequency.[3,5,6] Although middle latency auditory evoked potentials (MLAEP) have been reported to correlate well with anaesthetic depth[7] and to be able to demonstrate potential awareness,[8,9] MLAEP are usually obtained intermittently and the waveforms are difficult to use in the clinical situation. More recently, the auditory evoked potential index (formerly known as the level of arousal score), derived from auditory evoked potentials, has been proposed as a single numerical variable for monitoring depth of anaesthesia.[10-12] The auditory evoked potential index reflects the morphology of the auditory evoked potential curves and is calculated from the amplitude difference between successive segments of the curve. A moving time average of the auditory evoked potential index is obtained at 3-s intervals.

The purpose of this study was to compare the four variables, bispectral index, median frequency, 95% spectral edge frequency and auditory evoked potential index, recorded simultaneously during emergence from propofol anaesthesia. In this situation, propofol concentrations in the brain would change in parallel with those in blood. We studied the correlation of the four variables with calculated blood concentrations of propofol, as a substitute for brain concentrations. The ability of the four variables to distinguish consciousness from unconsciousness was also investigated.

## Patients and methods

After obtaining approval from the Ethics Committee and informed consent, we studied 10 female patients undergoing minor surgery: five for diagnostic laparoscopy, four for ligation of varicose veins and one for hysteroscopy. Mean age was 31.2 (range 17–49) yr and mean weight 60.9 (47–72) kg.

All patients were unpremedicated and had been fasted for at least 6 h. A single dose of fentanyl 50–75 µg was given immediately before induction of anaesthesia. Anaesthesia was induced and maintained with target-controlled infusions of propofol[13] and a laryngeal mask was inserted. The target-controlled infusion system was operated by a three-compartment pharmacokinetic model "Diprifusor". Mean

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values of minimum and maximum target blood concentrations of propofol during anaesthesia were 3.8 (range 2–5) and 9.6 (6–14) μg $ml^{-1}$, respectively. Anaesthesia was supplemented with 66% nitrous oxide in oxygen and ketorolac 10 mg i.v. Patients breathed spontaneously throughout the study. After discontinuation of propofol infusion and nitrous oxide inhalation, patients were prompted verbally to open their eyes. The observer was unaware of the values being measured. Consciousness was deemed to be present when patients opened their eyes to command.

### SURFACE EEG ANALYSES

The EEG was obtained from four disposable silver–silver chloride electrodes (Zipprep, Aspect Medical Systems, MA, USA) placed on both sides of the outer malar bone (At1 and At2), with Fpz as the reference and Fp1 as the ground. Impedance of the electrodes was confirmed to be less than 2000 Ω. Bispectral index, median frequency and 95% spectral edge frequency were measured using an EEG monitor (A-1000, BIS 3.0 algorithm, rev. 0.40 software, Aspect Medical Systems, MA, USA). Bispectral index, median frequency and 95% spectral edge frequency required at least 30 s to be fully updated. Data were stored automatically on a microcomputer (T1950CT, Toshiba, Japan) at 5-s intervals. The EEG before induction of anaesthesia was obtained when the patient's eyes were closed.

### AUDITORY EVOKED POTENTIALS ACQUISITION

Auditory evoked potentials (AEP) were obtained using a similar system to that described in our previous study[8] from three electrodes (Zipprep) placed at the right mastoid (+), and middle forehead (−), with Fp2 as the reference. The amplifier was custom-built with a 5 kV medical grade isolation. It had a common mode rejection ratio of 170 dB with balanced source impedance, input voltage noise of 0.3 μV (10 Hz–1 kHz rms) and current input noise of 4 pA (0.05 Hz–1 kHz rms). A third-order Butterworth analogue band-pass filter with a bandwidth of 1–220 Hz was used. The clicks were 70 dB above the normal hearing level and had a duration of 1 ms. They were presented at a rate of 6.9 Hz to both ears. The amplified EEG was sampled at a frequency of 1778 Hz by a 12-bit analogue-to-digital converter (PCM-DAS08, Computer Boards Inc., MA, USA) and was processed in real-time by the microcomputer. Auditory evoked potentials were produced by averaging 256 sweeps of 144 ms duration. The time required for a full update of the signal was 36.9 s, but a moving time averaging technique allowed a faster response time to any change in the signal. The auditory evoked potentials were obtained at 3-s intervals. The auditory evoked potential index is a mathematical derivative reflecting morphology of the AEP. The value was calculated as the sum of the square root of the absolute difference between every two successive 0.56-ms segment of the AEP waveform.[12]

Each variable was recorded simultaneously and mean values were obtained at intervals of 15 s. Mean values of the four variables were analysed using linear regression analysis against the calculated blood propofol concentration simulated by the "Diprifusor" pharmacokinetic model[13] during the emergence phase of anaesthesia, after discontinuation of propofol infusion and nitrous oxide inhalation until eye opening. The 95% prediction bands of the values were also obtained. Minitab for Windows was used for statistical analysis. Mean values obtained in the 15-s period just before induction of anaesthesia and those in the 15-s period just after eye opening to command were compared with the 95% prediction band. Values before induction and after eye opening were also compared with values just before eye opening using the Kruskal–Wallis and Tukey's tests. $P<0.05$ was considered statistically significant.

## Results

Mean duration of surgery and anaesthesia were 13.3 (range 5.5–30.2) min and 28.6 (18.6–46.1) min, respectively. Mean time interval from discontinuation of propofol infusion and nitrous oxide inhalation until eye opening was 8.6 (6.6–12.5) min. Mean calculated propofol concentration in blood at the time of eye opening was 1.9 (1.3–2.2) μg $ml^{-1}$.

Bispectral index values before eye opening correlated well with the calculated blood concentration of propofol (fig. 1). All bispectral index values before induction of anaesthesia and all values after eye opening were distributed in the 95% prediction band of the values before eye opening. Mean bispectral index values before and after eye opening did not differ from each other, but were significantly smaller than before induction of anaesthesia (fig. 5).

The 95% spectral edge frequency values before eye opening also correlated well with the calculated blood concentration of propofol (fig. 2). Although

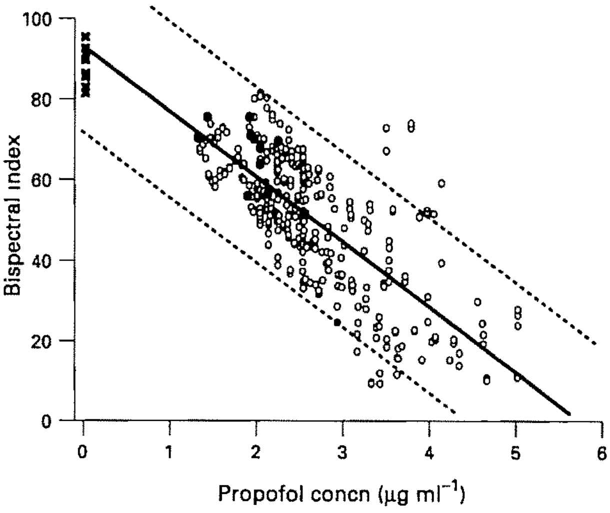

*Figure 1* Calculated propofol blood concentration *vs* bispectral index (○=before eye opening; ●=after eye opening; ×=before induction of anaesthesia). The linear regression line with 95% prediction band was analysed between calculated propofol concentration and values before eye opening. Bispectral index before eye opening was linearly related to propofol blood concentration (bispectral index=−12.8 (propofol)+93 6; $r=0.734$, $n=349$).

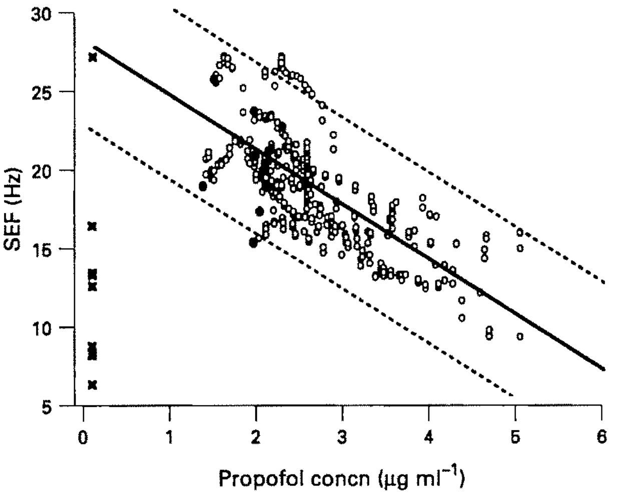

*Figure 2* Calculated propofol blood concentration *vs* 95% spectral edge frequency (SEF) (O=eye opening; ●=after eye opening; X=before induction of anaesthesia). The linear regression line with 95% prediction band was analysed between calculated propofol concentration and values before eye opening. The 95% SEF before eye opening was linearly related to propofol blood concentration (95% SEF=−3 44 (propofol)+27.9, $r$=0.686, $n$=349).

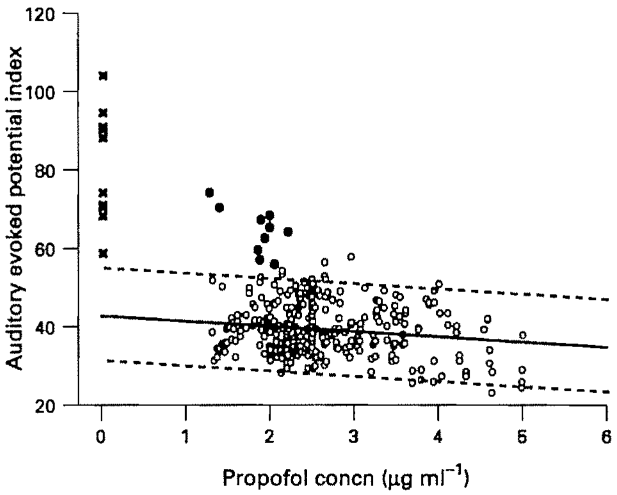

*Figure 4* Calculated propofol blood concentration *vs* auditory evoked potential index (O=before eye opening; ●=after eye opening; X=before induction of anaesthesia). The linear regression line with 95% prediction band was analysed between calculated propofol concentration and values before eye opening ($n$=349). The auditory evoked potential index before eye opening was not related to propofol blood concentration. The values after eye opening and before induction of anaesthesia were distributed above the prediction band and were well distinguished from those before eye opening.

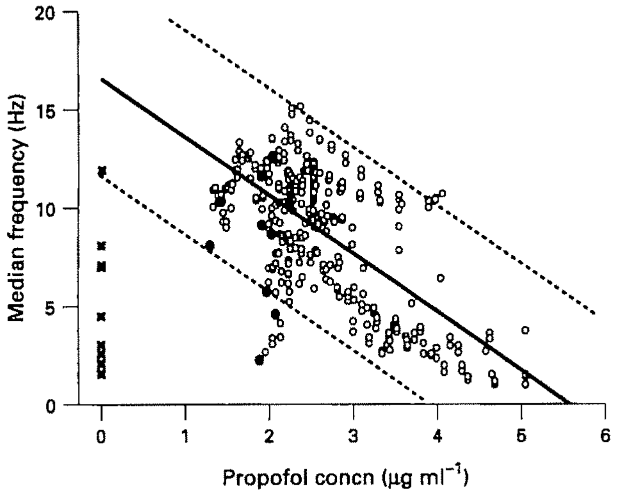

*Figure 3* Calculated propofol blood concentration *vs* median frequency (O=before eye opening; ●=after eye opening; X=before induction of anaesthesia). The linear regression line with 95% prediction band was analysed between calculated propofol concentration and values before eye opening. Median frequency before eye opening was linearly related to propofol blood concentration (median frequency=−2.98 (propofol)+16.5; $r$=0.647, $n$=349).

most of the values after eye opening were distributed within the 95% prediction band, those before induction of anaesthesia were spread widely below the band. The 95% spectral edge frequency values at a propofol blood concentration of zero had poor correlation with the regression line during anaesthesia. Mean 95% spectral edge frequency values just before and after eye opening were not different from each other, but significantly larger than before induction of anaesthesia (fig. 5).

Median frequency values before eye opening also correlated with blood concentrations of propofol (fig. 3). Values after eye opening were small and distributed below the regression line. Values before induction of anaesthesia were very small and spread mainly below 8 Hz, far below the prediction band. Median frequency values at a propofol blood concentration of zero showed poor correlation with the regression line during anaesthesia. There was no difference in mean median frequency values before induction of anaesthesia, before eye opening and after eye opening (fig. 5).

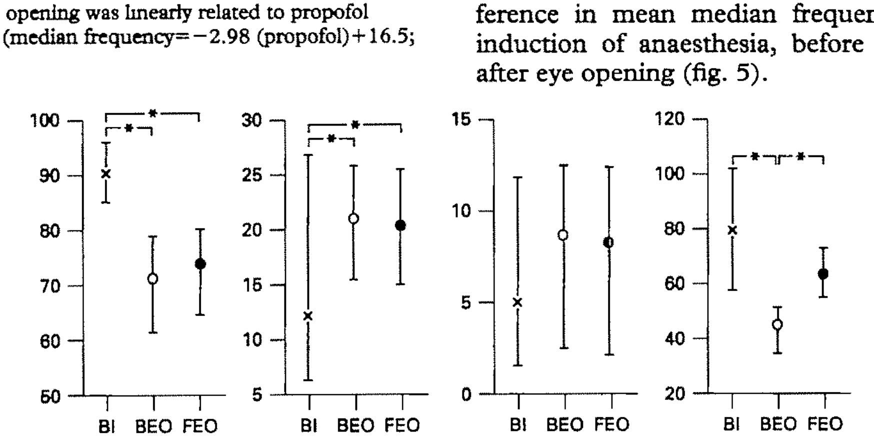

*Figure 5* Mean (range) values of the four variables at three periods: before induction of anaesthesia (BI, X), just before eye opening (BEO, O) and just after eye opening (FEO, ●) ($n$=10). *$P<0.05$ between two values.

Although auditory evoked potential indexes did not correlate with blood propofol concentrations before eye opening, they were distributed closely around 40, between blood propofol concentrations of 1 and 5 μg $ml^{-1}$, before recovery of consciousness. Auditory evoked potential indexes after eye opening and those before induction of anaesthesia were clearly distinguished from those before eye opening (fig. 4). There was no difference between values just before induction of anaesthesia and those recorded just after eye opening. Mean auditory evoked potential index before eye opening was significantly smaller than that after eye opening and also significantly smaller than that before induction of anaesthesia (fig. 5).

## Discussion

An appropriate performance measure is needed to evaluate and compare potential indicators of anaesthetic depth.[14] In this study, we examined four EEG variables using two methods: first, comparing values just before and after eye opening, and before induction of anaesthesia; second, investigating the correlation with calculated blood propofol concentrations. Eye opening is considered one of the "gold standard" indicators of anaesthetic depth during recovery. Blood propofol concentrations would be controversial as a indicator of anaesthetic depth because blood concentrations do not always reflect brain concentrations. This study was limited to the period during emergence from anaesthesia after discontinuation of propofol infusion. Although it was not a steady state, propofol concentrations in the brain would change in parallel with those in blood, which minimizes the discrepancy of propofol concentrations between blood and effector sites.

Chassard and colleagues reported that although propofol had little effect on brainstem auditory evoked potentials, it markedly suppressed the MLAEP, even at low concentrations. They could not identify Pa or Nb at propofol concentrations of 1.6–2.44 μg $ml^{-1}$.[15] Thornton and colleagues also reported that propofol profoundly affected the MLAEP[7] and speculated that the MLAEP reflected the hypnotic component of an anaesthetic agent. However, they did not study the transition from unconsciousness to consciousness. In this study we observed low auditory evoked potential indexes during sleep which increased suddenly just after eye opening. This suggested that the auditory evoked potential index reflected the level of consciousness rather than blood concentration of propofol. The auditory evoked potential index may therefore be a reliable monitor to detect awareness during anaesthesia.

Leslie and colleagues[3] reported that the bispectral index was monotonically related to blood concentrations of propofol; this finding is compatible with our study. This suggests that the bispectral index reflects the effect of given blood concentration of propofol. However, bispectral index values at the time of recovery of consciousness vary among studies. Howell and colleagues[16] reported that bispectral index values at the time of recovery of consciousness were 79.7 (SEM 3) during emergence from propofol anaesthesia and 82.1 (2) during emergence from propofol and alfentanil anaesthesia. Flaishon, Sebel and Sigl[17] reported that unconsciousness was not observed above a bispectral index of 70 and no consciousness was observed below a value of 65. We observed the transition from unconsciousness to consciousness at bispectral index values of 64–80. Kearse and colleagues[18] also reported that the bispectral index value that predicts 95% probability of unconsciousness was 52. The results of these studies suggest that a patient may recover consciousness at a bispectral index value of 50–85, but with an increasing probability at a higher value of the index. Our study revealed that bispectral index values before and after eye opening were not different. This suggested that the bispectral index could not detect the transition from unconsciousness to consciousness, where consciousness was defined as response to command.

Although 95% spectral edge frequency has been used widely to assess depth of anaesthesia, it showed large variability at low blood propofol concentrations. The variability was larger than that reported by Schwender and colleagues,[19] however our finding was comparable with that of Leslie and colleagues.[3] In our study and that of Leslie and colleagues, some subjects had low 95% spectral edge frequency values of less than 10 Hz. This might result from measurement when the eyes were closed. Median frequency also showed large variability, especially at low blood propofol concentrations. The large variability when awake may make assessment of anaesthetic depth difficult. This study demonstrated that the bispectral index was superior to 95% spectral edge frequency and median frequency in this respect.

These three variables, bispectral index, 95% spectral edge frequency and median frequency, demonstrated different characteristics from the auditory evoked potential index. The former three variables were derived from the same two-channel surface EEG signals. They are considered to reflect mainly cerebral cortex activity. Therefore, they correlated with blood propofol concentrations during emergence from anaesthesia. In contrast, the auditory evoked potential index was calculated from 144 ms of auditory evoked potentials. It reflects overall responses to auditory stimuli from the brainstem to the cerebral cortex. Although we have not identified the components of the waveforms, the overall responses demonstrated the transition from unconsciousness to consciousness very sharply, which mirrors the clinical state.

Blood concentrations of propofol were not measured but were calculated using a pharmacokinetic model.[20] However, in a previous study using a target control infusion system with the pharmacokinetic model,[21] discrepancies between calculated and actual blood concentrations were small after discontinuation of propofol infusion. The bias (mean prediction error) was −2%, and precision (mean of individual absolute prediction errors) was 15.1%.

This study was performed after the end of surgery. Therefore, the relationship between blood propofol concentration and the variables was not affected by the variable levels of surgical stimulation.[22]

Inhalation of nitrous oxide was discontinued at the same time as cessation of propofol infusion. Although the effects of nitrous oxide on auditory evoked potentials are weak,[23] a simultaneous decrease in nitrous oxide tension could influence the results. This study, therefore, could not determine the absolute relationship between propofol blood concentrations and the four variables; auditory evoked potential index or bispectral index required 36.9 s or 30 s, respectively, to be fully updated. Values measured 15 s after eye opening, therefore, included some components of values obtained before eye opening.

Within these limitations, we found different characteristics of the four variables for monitoring depth of anaesthesia. The variables processed from the surface EEG (bispectral index, 95% spectral edge frequency and median frequency) generally reflected blood concentrations of propofol. Of the three variables, bispectral index changed most linearly with propofol concentrations in blood. Therefore, bispectral index may provide the best prediction of recovery of consciousness during emergence from anaesthesia at the end of surgery.

Median frequency and 95% spectral edge frequency changed linearly when patients were unconscious, but lost the linearity during consciousness. Bispectral index was superior to median frequency and 95% spectral edge frequency. The auditory evoked potential index was different from the surface EEG derivatives and was the best variable to distinguish the transition from unconsciousness to consciousness.

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We thank Dr Joan Prentice and Dr Douglas Russell for their assistance.

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*British Journal of Anaesthesia* 1997; **78**: 185–188

LABORATORY INVESTIGATIONS

# Do local anaesthetics interact with dihydropyridine binding sites on neuronal L-type $Ca^{2+}$ channels?†

K. HIROTA, T. BROWNE, B. L. APPADU AND D. G. LAMBERT

## Summary

We have examined the interaction of procaine, prilocaine, lignocaine, bupivacaine, amylocaine and R(+) and S(−) ropivacaine with L-type voltage-sensitive $Ca^{2+}$ channels in rat cerebrocortical membranes. Membranes were prepared in Tris HCl 50 mmol litre$^{-1}$, pH 7.4, by homogenization and centrifugation. Binding assays were performed in 1-ml volumes of Tris HCl 50 mmol litre$^{-1}$, pH 7.4, for 90 min at room temperature using approximately 200 μg of protein. Non-specific binding was defined in the presence of nifedipine $10^{-5}$ mol litre$^{-1}$, and bound and free radioactivity were separated by vacuum filtration. The effects of local anaesthetics were determined by displacement of [$^3$H]PN200-110 (approximately 0.2 nmol litre$^{-1}$), a radiolabelled 1,4- dihydropyridine (DHP) L-channel antagonist. The concentration of displacer producing 50% displacement was corrected for the competing mass of [$^3$H]PN200-110 to yield the affinity constant, $K_{50}$. All local anaesthetics displaced [$^3$H]PN200-110 in a dose-dependent manner with a rank order potency of ($K_{50}$, mmol litre$^{-1}$) bupivacaine (0.48), amylocaine (0.74), lignocaine (1.09), prilocaine (2.06) and procaine (2.09). Ropivacaine enantiomers did not show stereoselective displacement, with $K_{50}$ values of 0.99 and 0.92 mmol litre$^{-1}$ for R(+) and S(−) ropivacaine, respectively. There was a significant correlation between p$K_{50}$ and p (octanol:buffer partition coefficient) ($r^2$=0.872, $P$=0.020), p$K_{50}$ and p (local anaesthetic potency) ($r^2$=0.816, $P$=0.036), p$K_{50}$ and p (relative conduction blocking potency) ($r^2$=0.843, $P$=0.028) and between p$K_{50}$ and p ($IC_{50}$ for inhibition of cardiac output) ($r^2$=0.897, $P$=0.015). These data suggest that DHP binding sites may be involved in both the mechanism of local anaesthesia and the cardiotoxicity of these agents. (*Br. J. Anaesth.* 1997; **78**: 185–188)

**Key words**
Anaesthetics local. Ions, ion channels. Ions, calcium. Model, rat.

It is well known that local anaesthetic agents inhibit voltage-sensitive $Na^+$ channels.[1–4] However, several studies[5–9] have suggested that clinically relevant concentrations of these agents also interact with voltage-sensitive $Ca^{2+}$ channels (VSCC) although the interaction may be weaker.[8] In an electrophysiological study, Sugiyama and Muteki[9] reported that the rank order of high voltage-activated (HVA) calcium current ($I_{Ca}$) inhibition was similar to their clinical rank order of potency. Moreover, Omote and colleagues[10] reported that the L-type VSCC blocker, verapamil, potentiated spinal anaesthesia induced by local anaesthetics. We have shown recently that a range of i.v. anaesthetic agents interact with 1,4-dihydropyridine (DHP) binding sites on L-type VSCC and suggested that this site may be a target for anaesthetic agents.[11]

In this study we have examined if a range of local anaesthetic agents (procaine, prilocaine, lignocaine, bupivacaine, amylocaine and R(+)/S(−)ropivacaine) interact with the DHP binding site in rat cerebrocortical membranes.

## Materials and methods

### TISSUE PREPARATION

Female Wistar rats (250–300 g) were stunned, decapitated and then the brain rapidly removed. The cerebral cortex was detached from its internal structures, placed in Tris HCl 50 mmol litre$^{-1}$, pH 7.4, at 4 °C and homogenized using a tissue tearer (setting 5, 5×30-s bursts). The homogenate was centrifuged at 18 000×$g$ for 10 min and the pellet resuspended in Tris HCl buffer. This procedure was repeated three times. The crude cell membrane preparation was frozen in aliquots at −40 °C.

### MEASUREMENT OF [$^3$H]PN200-110 BINDING

All binding assays[12] were performed in 1-ml volumes of Tris HCl buffer for 90 min at 20 °C using cerebrocortical membranes containing approximately 200 μg of protein. Non-specific binding was defined

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in the presence of excess nifedipine ($10^{-5}$ mol litre$^{-1}$).[11] After incubation, each sample was filtered under vacuum through Whatman GF/B filters using a Brandel cell harvester to separate bound and free radioactivity. Filter retained (bound) radioactivity was extracted for at least 8 h in 4 ml of scintillation fluid before estimation using a β-scintillation counter. Estimated radioactivity was quench corrected with an average [$^3$H] counting efficiency of 60.4%. In order to determine if local anaesthetics interacted with DHP binding sites on L-type Ca$^{2+}$ channels, the DHP binding site was labelled with [$^3$H]PN200-110. Increasing concentrations of unlabelled displacer (local anaesthetics) were then added. Displacement of [$^3$H]PN200-110 binding by local anaesthetics indicates that they are interacting at the same site as the radiolabel. A fixed concentration of [$^3$H]PN200-110 (approximately 0.2 nmol litre$^{-1}$) was displaced by the following unlabelled agents ($n$=5–6 for each): bupivacaine $3\times10^{-5}$–$3\times10^{-3}$ mol litre$^{-1}$, lignocaine $10^{-4}$–$3\times10^{-2}$ mol litre$^{-1}$, prilocaine $10^{-4}$–$3\times10^{-2}$ mol litre$^{-1}$, procaine $10^{-4}$–$3\times10^{-2}$ mol litre$^{-1}$, amylocaine $3\times10^{-5}$–$10^{-2}$ mol litre$^{-1}$ and ropivacaine optical isomers, R(+) and S(−) ropivacaine $10^{-6}$–$3\times10^{-2}$ mol litre$^{-1}$. Local anaesthetic stock solutions were prepared in distilled water at least 50 times higher than the top concentration required. All were then diluted in Tris HCl buffer. The highest concentration of bupivacaine used was limited by agent solubility. With the exception of ropivacaine which was a gift from Astra (Sweden), all local anaesthetic agents were purchased from Sigma Chemical Co Ltd (Poole, Dorset, UK).

### DATA ANALYSIS

Specific binding was calculated as the difference between total and non-specific binding. Concentrations of displacer producing 50% displacement of specific binding were obtained by computer-assisted curve fitting (Graphpad-Prism) and corrected for the competing mass of [$^3$H]PN200-110 to yield the affinity constant ($k_{50}$ presented as $\log_{10} K_{50}$, i.e. p$K_{50}$) using a $K_d$ of 59 pmol litre$^{-1}$ obtained previously.[11] All data are expressed as mean (SEM) and displacement curves were drawn after correction for the competing mass of [$^3$H]PN200-110 for the whole curves.

## Results

All local anaesthetics displaced specific [$^3$H]PN200-110 binding in a dose-dependent manner (fig. 1A) with p$K_{50}$ values shown in table 1. The rank order of displacement was bupivacaine>amylocaine>lignocaine>prilocaine>procaine. There was a significant correlation between p$K_{50}$ and p (anaesthetic potency), p (conduction block), p (lipid solubility) and p (dose (mol kg$^{-1}$) required to reduce cardiac output by 50%).

Both ropivacaine optical isomers displaced [$^3$H]PN200-110 binding in a dose-dependent manner, with estimated p$K_{50}$ values of 3.005 (0.104) (987 μmol litre$^{-1}$) for R(+) and 3.036 (0.109) (920

*Table 1* Effects of local anaesthetics on [$^3$H]PN200-110 binding. Data are mean (SEM) ($n$=6)

| Local anaesthetic | p$K_{50}$ [mean $K_{50}$] (mmol litre$^{-1}$) |
|---|---|
| Procaine | 2.680 (0.039) [2.09] |
| Prilocaine | 2.687 (0.010) [2.06] |
| Lignocaine | 2.962 (0.095) [1.09] |
| Amylocaine | 3.129 (0.030) [0.74] |
| Bupivacaine | 3.317 (0.019) [0.48] |

*Table 2* Correlation between p$K_{50}$ for [$^3$H]PN200-110 binding, local anaesthetic potency, relative conduction blocking potency, octanol:buffer partition coefficient and IC$_{50}$ for cardiac output. (Local anaesthetic and conduction blocking potency can be found in Strichartz and Berde.[4] Octanol:buffer partition coefficient at pH 7.4 and 25°C can be found Strichartz and colleagues[13])

| Correlation | $r^2$ | $P$ |
|---|---|---|
| p$K_{50}$ *vs* p (local anaesthetic potency) | 0.816 | 0.036 |
| p$K_{50}$ *vs* p (relative conduction blocking potency) | 0.843 | 0.028 |
| p$K_{50}$ *vs* p (octanol:buffer partition coefficient) | 0.872 | 0.020 |
| p$K_{50}$ *vs* p (IC$_{50}$ for cardiac output (mol kg$^{-1}$)) | 0.897 | 0.015 |

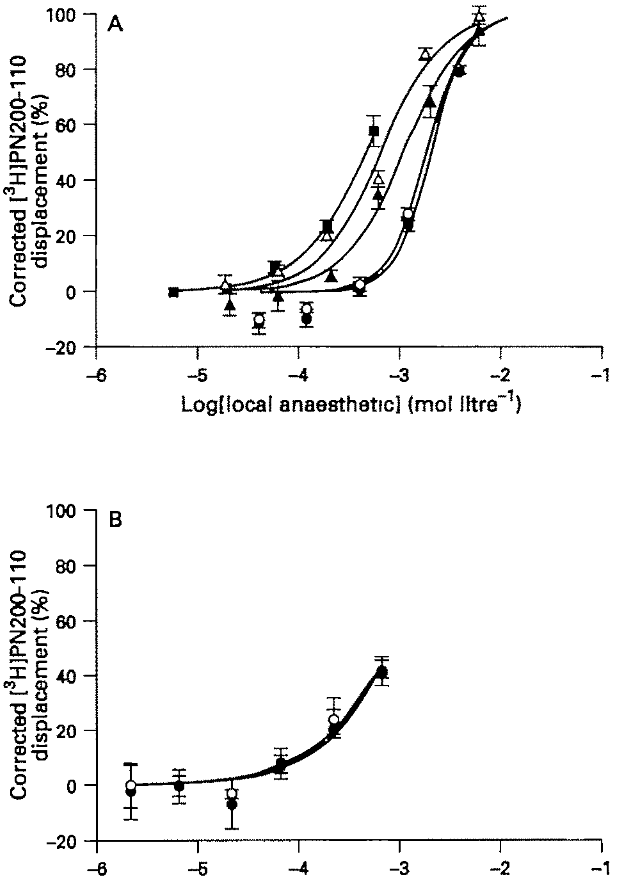

*Figure 1* A: Local anaesthetic agents dose-dependently displaced [$^3$H]PN200-110 binding to L-VSCC (●=procaine, ○=prilocaine, ▲=lignocaine, △=amylocaine and ■=bupivacaine). B: R(+) (●) and S(−) (○) ropivacaine displaced [$^3$H]PN200-110 binding in a dose-dependent manner but there was no stereoselectivity. Data are mean, SEM ($n$=5–6), expressed as corrected displacement where the curves have been corrected for the competing mass of [$^3$H]PN200-110.

$\mu$mol $\text{litre}^{-1}$) for S(−) (fig. 1B). In the case of ropivacaine where only 40% displacement was achieved, $pK_{50}$ values were estimated based on a theoretical 100% maximum displacement and were thus not included in any correlation calculations.

## Discussion

Local anaesthetics are well known to depress voltage-sensitive $Na^+$ channels, thereby blocking axonal conduction.[1–4] In this study we have demonstrated that a range of local anaesthetics dose-dependently inhibited [$^3$H]PN200-110 binding to L-type voltage-sensitive $Ca^{2+}$ channels. The concentration of anaesthetic producing 50% inhibition correlated with lipid solubility (octanol:buffer partition coefficient), anaesthetic potency, depression of cardiac output and conduction blocking potency.[4,13] In agreement with our data, Bolger and colleagues[7] reported that local anaesthetics displaced [$^3$H]nitrendipine binding (in an allosteric fashion) to rat brain and cardiac membranes, although they did not report a correlation between $K_{50}$ and partition coefficient. While we have not demonstrated this, we feel that local anaesthetic agents interact allosterically with the [$^3$H]PN200-110 binding site, and the "strength" of this allosterism is dependent on lipid solubility.

In addition to these radioligand binding studies there are several electrophysiological studies indicating that local anaesthetics depress high voltage-activated $Ca^{2+}$ currents (HVA-$I_{Ca}$), including DHP-sensitive ion movements.[5,6,8,9] Sugiyama and Muteki[9] suggested that inhibition of $Ca^{2+}$ influx through VSCC may contribute to spinal anaesthetic mechanisms as there is a good correlation between local anaesthetic potency and their ability to inhibit HVA-$I_{Ca}$. Moreover, lignocaine has been shown to inhibit depolarization evoked prolactin secretion from GH4C1 cells by inhibiting $Ca^{2+}$ influx, with an $IC_{50}$ value of approximately 0.25 mmol $\text{litre}^{-1}$.[14]

Also, a range of local anaesthetic agents have been reported to inhibit nicotinic receptor-mediated catecholamine release from bovine adrenal chromaffin cells.[15,16] Lee-Son and colleagues[3] found that local anaesthetics stereoselectively depressed neuronal $Na^+$ channels and Bolger and colleagues[7] also reported that the enantiomers of the experimental agent RAC-109 showed stereoselective inhibition of [$^3$H]nitrendipine binding in rat brain membranes. In this study we were unable to demonstrate a stereoselective interaction of ropivacaine enantiomers with rat cerebrocortical L-type VSCC. The lack of a stereospecific effect of ropivacaine enantiomers is difficult to explain and may question the importance of VSCC block in local anaesthetic action. However, as the isomeric differences in potency are usually small, the significance of these data is unclear. Collectively, our data suggest that L-VSCC block may be an additional mechanism of local anaesthetic action and support the general observation that L-type VSCC antagonists have antinociceptive properties.[17–19]

Accidental i.v. injection of local anaesthetic can precipitate cardiovascular collapse.[20,21] Cardiovascular toxicity of local anaesthetics results from a decrease in cardiac fast $Na^+$ channel activity.[20] In addition, modulation of cardiac $Ca^{2+}$ handling may also be implicated. Indeed, Lynch[22] suggested that depression of myocardial contractility produced by local anaesthetics may result from intracellular $Ca^{2+}$ release from the sarcoplasmic reticulum but not $Ca^{2+}$ entry, although cardiotoxic concentrations of local anaesthetics[21] seemed to depress $Ca^{2+}$ entry. In our study, a significant correlation between $pK_{50}$ and $pIC_{50}$ for cardiac output[4] was found, although it should be emphasized that in this study we used cerebrocortical membranes.

In conclusion, this study demonstrated an interaction between local anaesthetic agents and L-VSCC and this may contribute to the cardiotoxicity of local anaesthetic agents.

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# Effect of halothane on conventional protein kinase C translocation and down-regulation in rat cerebrocortical synaptosomes

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## Summary

Protein kinase C (PKC) is a key regulatory enzyme that has been implicated as a molecular target for the action of general anaesthetics. We have determined the effects of halothane on the translocation and down-regulation of conventional PKC (cPKC) by analysing the subcellular distribution of PKC activity, [$^3$H]phorbol-12,13-dibutyrate ([$^3$H]PDBu) binding and PKC immunoreactivity in intact rat cerebrocortical synaptosomes, a subcellular fraction that contains functional nerve terminals. Halothane alone (2.4 vol%) reduced membrane-associated ($P<0.05$) and increased cytosol ($P<0.01$) PKC activity, while phorbol-12-myristate, 13-acetate (PMA) 0.1 μmol litre$^{-1}$, a metabolically stable activator of PKC, reduced membrane ($P<0.01$) without altering cytosol PKC activity. Halothane and PMA in combination reduced membrane PKC activity to undetectable levels and reduced cytosol PKC activity ($P<0.01$). Halothane alone had no significant effects on the distribution of [$^3$H]PDBu binding, while PMA alone significantly reduced both membrane and cytosol [$^3$H]PDBu binding ($P<0.01$). Halothane and PMA in combination reduced membrane and cytosol [$^3$H]PDBu binding further, but this effect was not significantly different from the effect of PMA alone. Experiments using isoform-selective antibodies to PKC$\alpha$, PKC$\beta$ or PKC$\gamma$ demonstrated synergistic interactions between halothane and PMA in promoting translocation of the three conventional PKC isoforms from the cytosol to the membrane fraction of synaptosomes and down-regulation of their immunoreactivity. Halothane and PMA together reduced cytosol PKC$\alpha/\beta/\gamma$ immunoreactivity significantly more ($P<0.05$) than PMA alone. Halothane thus has two distinct actions on PKC in synaptosomes: activation of endogenous PKC activity and potentiation of activation-induced cPKC translocation and down-regulation. These potentially competing effects may underlie some of the conflicting results obtained with halothane on PKC-mediated processes in intact cells. (*Br. J. Anaesth.* 1997; **78**: 189–196)

**Key words**

Anaesthetics volatile, halothane. Enzymes, protein kinase C. Nerve, synaptosomes. Rat.

Protein kinase C (PKC) is an important family of protein kinases that regulates neuronal function.[1,2] Many studies have implicated PKC as a potential target for general anaesthetic effects in various tissues.[3–17] PKC exists as a number of structurally related isoforms distinguished by their regulatory domains and cofactor dependence[18–20]: the conventional PKC isoforms (cPKC: $\alpha$, $\beta1$, $\beta2$ and $\gamma$) are activated by Ca$^{2+}$, diacylglycerol and phorbol esters; the new PKC isoforms (nPKC: $\delta$, $\epsilon$, $\eta$ and $\theta$) do not require Ca$^{2+}$ but are activated by diacylglycerol and phorbol esters; and the atypical PKC isoforms (aPKC: $\zeta$, $\lambda$, $\mu$ and PKC$_\iota$) do not require Ca$^{2+}$ or diacylglycerol for activity and are not affected by phorbol esters.

Physiological activation of cPKC isoforms, which are abundant in mammalian brain,[19] occurs when diacylglycerol is generated in response to activation of cell surface receptors coupled to activation of phospholipase C or in response to Ca$^{2+}$-induced activation of phospholipase D.[1,21] Binding of diacylglycerol increases the affinity of cPKC for Ca$^{2+}$ and phosphatidylserine, facilitates cPKC translocation and binding to cell membranes, and increases cPKC catalytic activity.[22] Phosphorylation of specific proteins by activated PKC is the effector mechanism for regulation of several neuronal processes,[2] many of which are also sensitive to general anaesthetics, such as neurotransmitter release,[23] ion channel function[24] and neurotransmitter receptor desensitization.[25] On agonist-induced stimulation of a number of cell types, cPKC and nPKC, but not aPKC, isoforms[26] rapidly translocate from the cytosol to the membrane where they undergo proteolysis-mediated down-regulation in an isoform-specific manner.[27,28] The role of these important regulatory mechanisms in determining the ultimate effects of anaesthetics and other drugs on the PKC signalling pathway in specific tissues and cells is unknown.

Previous studies of general anaesthetic effects on PKC activity have yielded contradictory results. For example, halothane has been found to inhibit[13] or stimulate[14] purified brain PKC *in vitro*, and to

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stimulate PKC activity in brain cytosol,[6] in synaptosomes[15] and in intact neurosecretory cells.[9] These differences may be explained in part by variations in the conditions used to analyse PKC activity *in vitro*,[14] or by differences in the particular PKC isoforms present. PKC has been implicated in the effects of general anaesthetics on neurotransmitter release from PC12 cells,[9] prostacyclin production in endothelial cells,[16] protein phosphorylation in neuronal growth cones,[12] smooth muscle contraction,[10] hepatic blood flow[17] and loss of righting reflex in tadpoles.[11] Several of these studies inferred anaesthetic inhibition, rather than activation, of PKC activity based on indirect evidence. We now report evidence that halothane can potentiate cPKC translocation and down-regulation induced by phorbol ester treatment in synaptosomes. The results provide a potential mechanism for biphasic effects of halothane on PKC activity in intact cells: initial stimulation of PKC activity as a result of a direct effect on enzymatic activity,[15] followed by alterations in PKC-dependent processes caused by PKC translocation and down-regulation.

## Materials and methods

### SYNAPTOSOME PREPARATION AND INCUBATION

Synaptosomes were prepared from rat cerebral cortex by the method of Dunkley, Jarvie and Heath,[29] as described previously,[30] and were stored as pellets on ice for up to 4 h until use. Synaptosome pellets were resuspended to a protein concentration of 2 mg $ml^{-1}$ (determined by the method of Bradford[31] with bovine serum albumin as standard) in incubation medium containing the following (mmol $litre^{-1}$): NaCl 140, KCl 5, $NaHCO_3$ 5, $MgCl_2$ 1, D-glucose 10 and HEPES (4-(2-hydroxyethyl)-1-piperazine ethanesulphonic acid) 10, at pH 7.4 with NaOH containing 1 mg $ml^{-1}$ of fatty acid-free bovine serum albumin) equilibrated with 95% oxygen–5% carbon dioxide (v/v). After a 5-min incubation period in a shaking water bath at 37 °C to allow ion gradient re-equilibration, $CaCl_2$ 1 mmol $litre^{-1}$ was added to a 1-ml aliquot of synaptosomes. After another incubation period of 1 min, halothane, phorbol-12-myristate, 13-acetate (PMA) or drug vehicle (dimethyl sulphoxide; DMSO) was added where appropriate. Translocation reactions were carried out in 8.8 ml glass vials sealed with Teflon/silicone septa, through which liquid halothane (1–2 μl, either pure or diluted with DMSO, injected onto the side of the vial to vaporize) was injected directly with a Hamilton microsyringe. Final vapour phase halothane concentrations, which equilibrate by 2 min,[32] were measured in similar samples by gas chromatography.[33] The incubation was continued for another 10 min, after which the reaction mixtures were transferred rapidly to polycarbonate centrifuge tubes on ice and centrifuged at 9000×*g* for 5 min at 4 °C.

### SYNAPTOSOME FRACTIONATION

After incubation synaptosomes were fractionated by a modification of the method of Díaz-Guerra and colleagues.[34] The synaptosome pellet was lysed immediately in 2 ml of ice-cold hypotonic lysis buffer (HEPES 10 mmol $litre^{-1}$, pH 7.4, with NaOH, EGTA 1 mmol $litre^{-1}$, EDTA 1 mmol $litre^{-1}$, dithiothreitol 1 mmol $litre^{-1}$, leupeptin 1 μg $ml^{-1}$) by homogenization with a glass/Teflon homogenizer for five up-and-down strokes. The homogenate was centrifuged at 200 000×*g* for 15 min at 4 °C to yield supernatant ("cytosol") and pellet ("membrane") fractions, which were separated. The pellet fraction was resuspended in 1 ml of lysis buffer containing 0.5% (v/v) Nonidet P-40 by homogenization and incubated on ice for 30 min to extract PKC activity. An additional 1 ml of lysis buffer was added to dilute the detergent concentration, the pellet was centrifuged at 200 000×*g* for 15 min at 4 °C, and the supernatant fraction ("membrane extract") was removed. The cytosol and membrane extract fractions were then filtered through 1-ml (bed volume) columns of DEAE-cellulose (DE-52, Whatman) equilibrated in lysis buffer to remove endogenous PKC inhibitors[35] and detergent. The columns were washed with 4 ml of lysis buffer, followed by 2 ml of lysis buffer containing NaCl 0.1 mol $litre^{-1}$ to elute PKC activity. The samples containing PKC were then concentrated and their buffer changed to HEPES 10 mmol $litre^{-1}$, pH 7.5, with a Centricon-30 concentrator (Amicon, Inc., Beverly, MA, USA) The concentrated samples were adjusted to equal volumes and protein concentrations were measured by the method of Bradford.[31] Protein recoveries were comparable between the different treatments. Aliquots were stored frozen at −80 °C until analysis.

### PKC ACTIVITY

The activity of PKC in the synaptosome extracts was measured at 30 °C in a reaction volume of 0.1 ml containing HEPES 50 mmol $litre^{-1}$, pH 7.4, with NaOH, $MgCl_2$ 10 mmol $litre^{-1}$, bovine serum albumin 20 μg $ml^{-1}$ (fraction V; Baker, Phillipsburg, NJ, USA), dithiothreitol 0.1 mmol $litre^{-1}$, [$\gamma$-$^{32}$P]ATP 100 μmol $litre^{-1}$ (100–250 cpm $pmol^{-1}$; DuPont-NEN, Boston, MA), lysine-rich histone H1 0.2 mg $ml^{-1}$ (9.3 μmol $litre^{-1}$) (histone HL; Worthington Biochemical, Freehold, NJ, USA), an aliquot of synaptosome extract (protein 0.25–10 μg), $CaCl_2$ 1.5 mmol $litre^{-1}$, EGTA 1 mmol $litre^{-1}$ (free [$Ca^{2+}$]=500 μmol $litre^{-1}$), and small unilamellar lipid vesicles composed of bovine brain L-α-phosphatidylserine 20 μmol $litre^{-1}$ (PS; Avanti Polar Lipids, Alabaster, AL, USA), chicken egg L-α-phosphatidylcholine (PC; Avanti Polar Lipids) 80 μmol $litre^{-1}$ and 1,2-dioleoyl-sn-glycerol (Avanti Polar Lipids) 2 μmol $litre^{-1}$ prepared as described previously.[14] The reaction mixture, containing all assay components except ATP, was equilibrated for 5 min, after which reactions were initiated by addition of ATP and terminated after 5 min by addition of glacial acetic acid 10 μl. Histone phosphorylation was determined by the phosphocellulose paper method as described previously.[14] At least two concentrations of each synaptosome extract were analysed to ensure that the reaction was in the linear range. Each assay was performed in triplicate in the absence and presence of the selective PKC inhibitor peptide $PKC_{19-36}$[36] at 10 μmol $litre^{-1}$. PKC activity was defined as the difference between histone kinase activity in the absence or presence of the PKC inhibitor (1 unit of activity=1 pmol $min^{-1}$ of $^{32}P$ incorporation into histone H1). Background phosphorylation in the absence of histone HI as a result of endogenous substrates was negligible.

### 4β-[$^3$H]PHORBOL-12,13-DIBUTYRATE BINDING

Binding of the phorbol ester 4β-[$^3$H]phorbol-12,13-dibutyrate (PDBu) to PKC was determined at 37 °C in a reaction volume of 0.1 ml containing HEPES 50 mmol $litre^{-1}$, pH 7.4, with NaOH, $MgCl_2$ 10 mmol $litre^{-1}$, EGTA 1 mmol $litre^{-1}$, $CaCl_2$ 1.5 mmol $litre^{-1}$, PS 20 μmol $litre^{-1}$, PC 80 μmol $litre^{-1}$ and [$^3$H]PDBu 0.1 μmol $litre^{-1}$ (0.2 μCi; DuPont-NEN). The reaction was initiated by addition of [$^3$H]PDBu, incubated for 15 min (sufficient for equilibration of binding; data not shown), and terminated by addition of 4 ml of ice-cold Tris 20 mmol $litre^{-1}$, pH 7.5, with HCl, $CaCl_2$ 200 μmol $litre^{-1}$ and 20% (v/v) methanol, followed by rapid filtration through polyethyleneimine-treated[37] GF/C filters (Whatman, Hillsboro, OR, USA), and then by three washes of 2 ml each with the same buffer. Protein-bound radioactivity retained on the filters was quantified by liquid scintillation spectrometry in 4 ml of Bio-Safe NA scintillant (Research Products International Corp., Mount Prospect, IL, USA). Non-specific binding, determined by inclusion of non-radioactive PDBu 10 μmol $litre^{-1}$, was negligible. These assays were saturated with respect to [$^3$H]PDBu concentration and provided a quantitative assay of the phorbol ester receptor as an index of PKC.[38] Residual PMA from the preincubation does not affect subsequent binding of [$^3$H]PDBu to membranes as these subcellular fractions are subjected to chromatography and washing by centrifugation.[37]

In a separate series of experiments, the effect of halothane on equilibrium [$^3$H]PDBu binding to synaptosomes was analysed using a range of [$^3$H]PDBu concentrations (10–200 nmol $litre^{-1}$). The dissociation constant ($K_d$) and maximum number of binding sites (Bmax) were calculated from Scatchard plots using the Enzfit kinetic program (Elsevier-Biosoft, Cambridge, UK).

### PKC IMMUNOBLOT ANALYSIS

Immunoreactive PKC was measured by immunoblotting of synaptosome extracts separated by sodium dodecyl sulphate/polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to nitrocellulose membranes. Cytosolic and membrane extracts were prepared as described above, but were not subjected to detergent extraction or DE-52 column chromatography. Aliquots (protein 20–60 μg) of the crude extracts were separated by SDS-PAGE using a 10% acrylamide running gel.[39] Proteins were transferred from gels to 0.2 μm nitrocellulose sheets (Schleicher and Schuell, Keene, NH, USA) at 0.2 amp for 20 h by the method of Towbin, Staehelin and Gordon.[40] The nitrocellulose sheets were blocked with 2.5% (w/v) non-fat dry milk (Carnation) and 0.05% (v/v) Tween 20 in PBS buffer (potassium phosphate 10 mmol $litre^{-1}$, pH 7.4, NaCl 150 mmol $litre^{-1}$, 0.02% (v/v) sodium azide) overnight. After a brief rinse in immunoblot buffer (PBS containing 0.2% (v/v) Tween 20), the nitrocellulose transfers were immunoblotted for 2 h with one of three specific mouse monoclonal antibodies to PKC in immunoblot buffer: (1) an antibody to rat brain PKCα used at a dilution of 1:5000 (Transduction Laboratories, Lexington, KY, USA; #P16520); (2) an antibody to human PKCβ used at a dilution of 1:2500 (Transduction Laboratories, #P17720); and (3) an antibody to rat PKCγ used at a dilution of 1:5000 (Transduction Laboratories, #P20420). The nitrocellulose transfers were then incubated successively with immunoblot buffer three times for 10 min, with rabbit anti-mouse secondary antibody in immunoblot buffer for 1 h (1:500 dilution; Pierce; Rockford, IL, USA), with immunoblot buffer five times for 5 min, with $^{125}$I-labelled protein A (1 μCi $ml^{-1}$; Amersham) in 2.5% non-fat dry milk and 0.05% Tween 20 in immunoblot buffer for 1.5 h, and with immunoblot buffer overnight followed by twice for 5 min. The PKC immunoreactive bands were examined by autoradiography and quantified by scanning and analysis with a PhosphorImager autoradiography system (Molecular Dynamics, Sunnyvale, CA, USA).

Thymol-free halothane was a gift from Halocarbon Products (River Edge, NJ, USA). The PKC inhibitor peptide ($PKC_{19-36}$),[36] synthesized by the Rockefeller University Protein Sequencing Facility, was a gift from A. J. Czernik (Rockefeller University). Nonidet P-40, Tween 20 and sodium dodecyl sulphate were from Pierce Chemical Co. (Rockford, IL, USA). PMA and PDBu were from LC Laboratories (Woburn, MA, USA). Bovine serum albumin (fatty acid-free) was from Sigma (St Louis, MO, USA).

### STATISTICAL ANALYSIS

Statistical significance was assessed by analysis of variance with the Newman–Keuls multiple range test using the PHARM/PCS Pharmacological Calculation System, v. 4.2 (Springer-Verlag, New York, NY).

The studies were approved by the Cornell University Medical College Institutional Animal Care and Use Committee.

## Results

### PKC ACTIVITY

The relative content of PKC enzymatic activity in fractionated rat cortical synaptosomes is shown in table 1. The synaptosomal membrane fraction contained a higher specific activity of PKC (defined as $PKC_{19-36}$-sensitive histone H1 activity) than the

*Table 1* Subcellular distribution of PKC in synaptosome exposed to phorbol ester and halothane. Intact synaptosome were incubated at 37°C for 10 min in the presence of 0.2% DMSO (control) or PMA 0.1 μmol litre$^{-1}$ and/or 2.4 vol% halothane with 0.2% DMSO, followed by synaptosome subfractionation as described in materials and methods. Data for PKC activity and [$^3$H]PDBu binding are mean (SD) of three independent experiments with individual assays performed in triplicate. U=unit (=pmol/min); ND=not detectable; PDBu=phorbol-12,13-dibutyrate; PMA=phorbol-12-myristate, 13-acetate; PKC=protein kinase C. *$P<0.05$ *vs* control; **$P<0.01$ *vs* control; †$P<0.05$ *vs* halothane; ††$P<0.01$ *vs* halothane; ‡$P<0.05$ *vs* PMA; ‡‡$P<0.01$ *vs* PMA

| | PKC acvitity | | [$^3$H]PDBu binding | |
|---|---|---|---|---|
| Treatment | U/mg | % Control | fmol/mg | % Control |
| Control | | | | |
| Cytosol | 1252 (110) | — | 2027 (86) | — |
| Membrane | 2425 (639) | — | 459 (29) | — |
| PMA | | | | |
| Cytosol | 1251 (256) | 100 | 140 (18)** | 7 |
| Membrane | 400 (221)** | 16 | 82.9 (53)** | 18 |
| Halothane | | | | |
| Cytosol | 3676 (1209)**‡‡ | 294 | 1983 (206)‡‡ | 98 |
| Membrane | 1538 (146)*‡‡ | 63 | 297 (78)‡ | 65 |
| Halothane+PMA | | | | |
| Cytosol | 311 (100)**††‡ | 25 | 102 (31)**†† | 5 |
| Membrane | ND | — | 66.3 (31)**† | 14 |

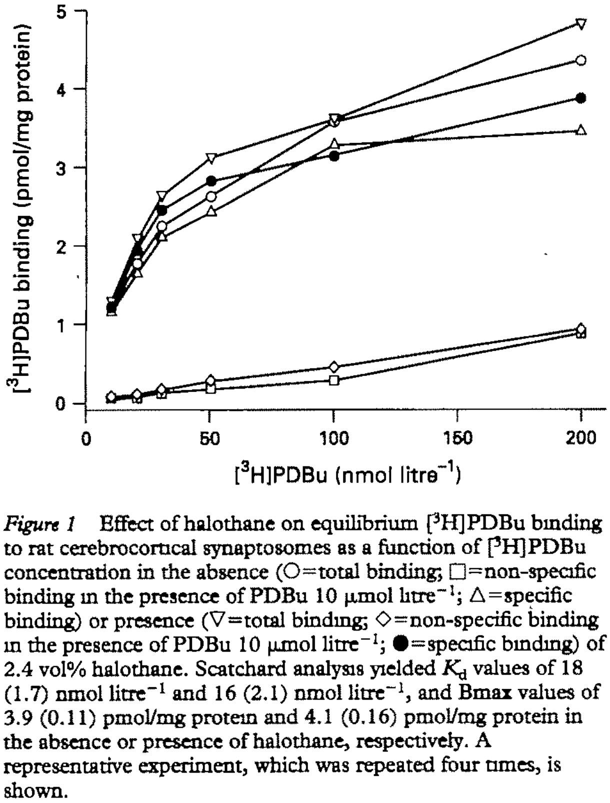

*Figure 1* Effect of halothane on equilibrium [$^3$H]PDBu binding to rat cerebrocortical synaptosomes as a function of [$^3$H]PDBu concentration in the absence (○=total binding; □=non-specific binding in the presence of PDBu 10 μmol litre$^{-1}$; △=specific binding) or presence (▽=total binding; ◇=non-specific binding in the presence of PDBu 10 μmol litre$^{-1}$; ●=specific binding) of 2.4 vol% halothane. Scatchard analysis yielded $K_d$ values of 18 (1.7) nmol litre$^{-1}$ and 16 (2.1) nmol litre$^{-1}$, and Bmax values of 3.9 (0.11) pmol/mg protein and 4.1 (0.16) pmol/mg protein in the absence or presence of halothane, respectively. A representative experiment, which was repeated four times, is shown.

cytosol fraction under basal conditions, which is consistent with the results of previous studies.[34 41] Treatment with phorbol esters has been shown to induce translocation of cytosolic PKC activity and down-regulation of membrane PKC activity in crude[27] and purified[34] synaptosomes. Exposure of intact purified synaptosomes to PMA 0.1 μmol litre$^{-1}$ for 10 min resulted in a significant reduction in membrane PKC activity with no change in cytosol PKC activity. Exposure of synaptosomes to 2.4 vol% halothane for 10 min also reduced membrane PKC activity, although not as much as PMA alone, but increased cytosol PKC activity. Exposure of synaptosomes to both PMA and halothane further reduced membrane PKC activity to undetectable levels and significantly reduced cytosol PKC activity compared with control, PMA alone or halothane alone.

### PHORBOL ESTER BINDING

Phorbol esters bind to the regulatory domains of and activate cPKC and nPKC, but not aPKC.[27 42] The effects of various treatments on the distribution of [$^3$H]PDBu binding sites in intact synaptosomes is shown in table 1. The cytosol fraction of rat cortical synaptosomes contained a four-fold excess of [$^3$H]PDBu binding sites compared with the membrane fraction. Exposure to PMA markedly reduced both membrane and cytosol [$^3$H]PDBu binding as a result of translocation and down-regulation.[27 34] The reduction in binding could be caused by residual PMA from the synaptosome preincubation competing with [$^3$H]PDBu binding, however, this effect has been reported to be reduced by anion exchange chromatography and washing before assay.[34] Exposure of synaptosomes to halothane had no significant effect on the subcellular distribution or amount of [$^3$H]PDBu binding. Treatment with a combination of both halothane and PMA reduced [$^3$H]PDBu binding to both the membrane and cytosol fractions, but this effect was not statistically different from treatment with PMA alone.

The effect of halothane on equilibrium binding of [$^3$H]PDBu was also assessed. A representative experiment is shown in figure 1. There was no significant difference between [$^3$H]PDBu binding to cerebrocortical synaptosomes in the absence ($K_d$=15 (SD 2) nmol litre$^{-1}$; Bmax=4.5 (1.1) pmol/mg protein) or presence ($K_d$=16 (7) nmol litre$^{-1}$; Bmax=4.7 (1.3) pmol/mg protein) of 2.4 vol% halothane ($n$=4).

### PKC IMMUNOREACTIVITY

Isoform-selective antibodies to PKC were used to determine the distribution of cPKCα, β and γ immunoreactive protein in control and treated synaptosomes by immunoblotting (fig. 2). All three

*Table 2* Subcellular distribution of conventional PKC isoforms in synaptosomes exposed to phorbol ester or halothane, or both. Intact synaptosome were incubated at 37°C for 10 min in the presence of 0.2% DMSO (control) or PMA 0.1 µmol litre$^{-1}$ and/or 2.4 vol% halothane with 0.2% DMSO, followed by synaptosome subfractionation as described in Materials and methods. Data are mean (SD) of one independent experiments with individual assays performed in triplicate. This experiment was repeated twice with similar results. AU=arbitrary units; U=unit (=pmol/min), PDBu=phorbol-12,13-dibutyrate; PMA=phorbol-12-myristate, 13-acetate; PKC=protein kinase C. *$P<0.05$ *vs* control; **$P<0.01$ *vs* control; †$P<0.05$ *vs* halothane; ††$P<0.01$ *vs* halothane; ‡$P<0.05$ *vs* PMA; ‡‡$P<0.01$ *vs* PMA

| | PKCα immunoreactivity | | PKCβ immunoreactivity | | PKCγ immunoreactivity | |
|---|---|---|---|---|---|---|
| Treatment | AU/ng | % Control | AU/ng | % Control | AU/ng | % Control |
| Control | | | | | | |
| Cytosol | 38.4 (4.4) | — | 2 06 (0.32) | — | 29.5 (7.6) | — |
| Membrane | 6.58 (0.58) | — | 0.15 (0.02) | — | 4.77 (0.33) | — |
| PMA | | | | | | |
| Cytosol | 4.43 (0.36)**†† | 12 | 0.25 (0.03)**†† | 12 | 9.76 (0 93)**†† | 33 |
| Membrane | 14.3 (1.0)**†† | 217 | 0.47 (0.08)**†† | 313 | 7 67 (0.09)**†† | 161 |
| Halothane | | | | | | |
| Cytosol | 33.2 (1.4)* | 86 | 2.95 (0.64)** | 143 | 25.6 (2.0) | 86 |
| Membrane | 5.30 (0.12)‡‡ | 80 | 0.10 (0.02)‡‡ | 67 | 4.62 (0.47) | 97 |
| Halothane+PMA | | | | | | |
| Cytosol | 0.22 (0.18)**††‡ | 0 5 | 0.014 (0.011)**††‡ | 1 | 0.56 (0.09)**††‡ | 2 |
| Membrane | 13 6 (0.5)**†† | 206 | 0.55 (0.04)**†† | 367 | 8 00 (0.63)**†† | 168 |

cPKC isoforms (PKCα, $M_r$=82 000; PKCβ, $M_r$=80 000; PKCγ, $M_r$=80 000) were enriched in the cytosol fraction compared with the membrane fraction under control conditions (table 2). The relative amounts of the three cPKC isoforms in purified rat cerebrocortical synaptosomes detected with these antibodies (PKCα>PKCγ>>PKCβ) do not reflect the actual relative amounts caused by differences in antibody cross-reactivity. Treatment with PMA induced both translocation of all three isoforms of PKC from the cytosolic to the membrane fraction (evident in the significant increase in membrane-associated PKC) and down-regulation of PKC (evident in the reduced cytosolic and total PKC). The effect of PMA on PKCγ was less marked. This is consistent with a previous study that showed PKCγ to be less sensitive to PMA-induced translocation and down-regulation than PKCα or PKCβ.[27] Halothane caused a small reduction in cytosolic PKCα and an increase in cytosolic PKCβ. Combined treatment with halothane and PMA resulted in synergistic reductions in the cytosolic levels of all three, cPKC isoforms. There were no significant changes in membrane levels, although total immunoreactivity was reduced; this indicates an increase in both translocation and degradation of PKC, as proteolysis occurs primarily with the membrane bound, and not the cytosolic, form of the enzyme.

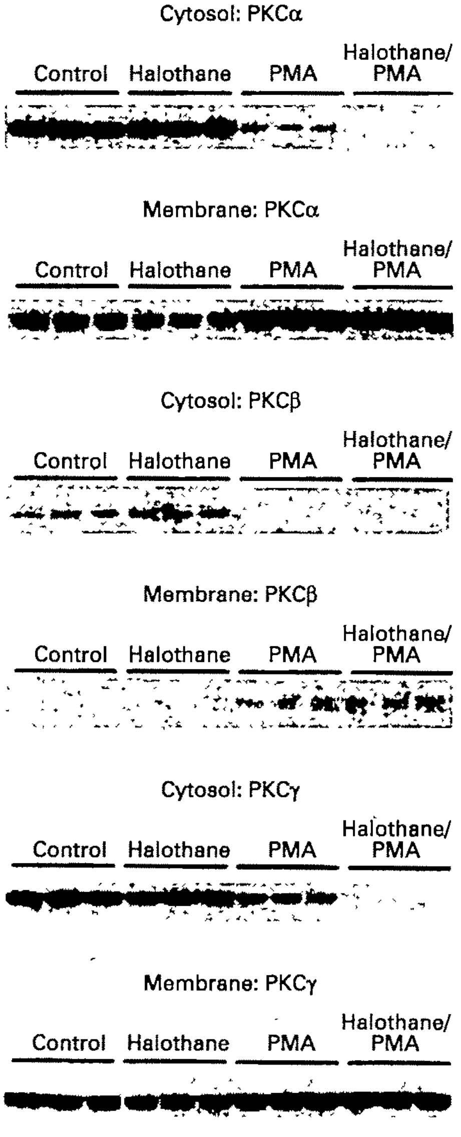

*Figure 2* Effects of halothane and phorbol ester on the subcellular localization of specific conventional PKC isoforms in rat cerebrocortical synaptosomes. Synaptosomes were incubated at 37°C for 10 min in the absence or presence of 2 4 vol% halothane, phorbol-12-myristate 13-acetate (PMA) 0.1 µmol litre$^{-1}$, or both, and separated into cytosolic and membrane fractions as described in the Materials and methods. Aliquots of each fraction (cytosol protein 20 µg; membrane protein 60 µg) in triplicate were separated by SDS-PAGE, transferred to nitrocellulose sheets and immunoblotted with antibodies to PKCα, PKCβ1 and PKCβ2, or PKCγ. PKC immunoreactivity was detected by the binding of $^{125}$I-labelled protein A and autoradiography (shown), and quantified by PhosphorImager analysis The portion of the immunoblot containing PKC immunoreactive bands ($M_r$=80–82 000) is shown for clarity; no other immunoreactive bands were identified.

## Discussion

Most neurones in the CNS contain the α, β and/or γ subspecies of the cPKC isoforms.[19,47] PKCα and

PKCβ are expressed in both CNS and peripheral tissues, while PKCγ is restricted to the brain and adrenal glands.[19] Within the CNS, PKCγ and PKCβ1 are found predominantly in nerve terminals and growth cones, while PKCγ and PKCβ2 are predominantly postsynaptic[19 43 44]; cortical synaptosomes contain PKCα, PKCβ and PKCγ.[44] The relative abundance and function of the nPKC or aPKC isoforms in synaptosomes have not been determined. Activation of PKC in synaptosomes or cultured neurones by diacylglycerol or tumour-promoting phorbol esters (long-acting agents that mimic the effects of diacylglycerol, which is rapidly metabolized) results in "translocation" of cPKC from the cytosol to the membrane fraction. Persistent activation of cPKC by diacylglycerol or phorbol esters results in "down-regulation" of PKC as a result of proteolysis with loss of enzyme activity and immunoreactivity. PMA causes an increase in particulate (membrane-associated) PKC activity ("translocation") at low doses (10 nmol litre$^{-1}$) followed by a dose- and time-dependent decrease in both cytosolic and particulate PKC activity ("down-regulation") in synaptosomes.[34]

Phorbol ester-induced translocation of cPKC in synaptosomes has been analysed previously by enzyme activity and phorbol ester binding measurements.[27 34] In this study we have compared the effects of phorbol ester or halothane, or both, on PKC translocation and down-regulation by three independent methods of PKC analysis: enzyme activity, phorbol ester binding and immunoblotting. Down-regulation of membrane PKC was the predominant effect of phorbol ester treatment observed for both PKC activity and [$^3$H]PDBu binding, while both translocation and down-regulation were observed for PKC immunoreactivity. Our results for the effects of phorbol ester on PKC activity and [$^3$H]PDBu binding generally agreed with those of previous studies.[27 34] Translocation of cPKC by phorbol ester has not been studied previously in synaptosomes by immunoblotting. However, comparable results have been reported by Chen and colleagues[42] in $C_6$ glioma cells in which 12-O-tetradecanoylphorbol 13-acetate 0.1 μmol litre$^{-1}$ induced a seven-fold increase in membrane PKCα and significantly reduced cytosolic PKCα. Of the three methods used to detect PKC, measurement of PKC immunoreactivity is the most direct method and least sensitive to artefacts,[28] although together they provide complementary information. Possible artefacts affecting measurement of PKC activity include the presence of endogenous PKC inhibitors,[35] non-linear reaction conditions, sub-optimal assay conditions, substrate accessibility and inadequate concentrations of the PKC inhibitor peptide. Possible artefacts affecting measurement of [$^3$H]PDBu binding include residual phorbol ester carried over from the preincubation with PMA (unlikely given the subcellular fraction preparation technique[34]) and the presence of endogenous phorbol ester binding competitors. Possible artefacts affecting measurement of PKC immunoreactivity include lack of antibody specificity and PKC degradation by proteolysis, the latter of which could also affect the two other methods. However, no immunoreactive breakdown products were detected in the immunoblots. Together these data indicate that caution is required in comparing the results of studies of PKC subcellular distribution determined by different methods.[28] The discrepancy between the activity measurements and [$^3$H]PDBu binding or immunoreactivity may reflect interactions between PKC and inhibitory regulatory protein(s) that modulate PKC activity in the membrane or cytosol, or both.[35]

We did not detect an effect of halothane on equilibrium [$^3$H]PDBu binding in synaptosomes. Activation of purified rat brain PKC by PDBu *in vitro* is also insensitive to halothane (unpublished observations). Our previous studies showed that halothane increases the sensitivity of PKC to activation by diacylglycerol, an endogenous PKC activator that binds to the same site in the regulatory domain of PKC as phorbol esters.[45] These results suggest that the interactions with PKC of phorbol esters and diacylglycerol differ in their sensitivity to halothane.

Halothane alone had no significant effects on PKC translocation or down-regulation measured by [$^3$H]PDBu binding or PKC immunoreactivity using the selective antibody to PKCγ. However, significant reproducible effects of halothane were observed on cytosol PKC activity and on cytosol PKCα and PKCβ immunoreactivity. Overall, the effects of 2.4 vol% halothane (which is close to its $EC_{50}$ for activation of purified PKC and is 2.3 times the MAC at 37 °C in rat[46]) on PKC distribution determined by the three methods were not consistent. In contrast, the combination of 2.4 vol% halothane and PMA 0.1 μmol litre$^{-1}$ consistently reduced cytosolic PKCα/β/γ immunoreactivity (increased PKC translocation) compared with treatment using PMA or halothane alone. The combination also reduced membrane PKC (increased PKC down-regulation) when measured by PKC activity, although this effect was not evident with [$^3$H]PDBu binding or the isoform-selective PKC antibodies. The enhanced translocation of PKC induced by halothane does not appear to involve a change in the ability of PKC to bind phorbol ester. This suggests that halothane stimulates the translocation process itself, perhaps by increasing the affinity of activated PKC for its membrane receptor.

We have shown previously that halothane and propofol stimulate purified PKC activity *in vitro*[14 45] and endogenous synaptosomal PKC activity *in situ*.[15] As prolonged stimulation of endogenous PKC with phorbol esters or diacylglycerol can promote cPKC translocation and down-regulation, we have analysed the effects of halothane on the subcellular distribution and down-regulation of cPKC in synaptosomes. Our results indicated that halothane alone had no significant effects on PKC translocation and down-regulation. The combination of halothane and the phorbol ester PMA resulted in significant potentiation of both translocation and down-regulation of synaptosomal PKC activity and immunoreactivity observed with PMA alone. These findings suggest that general anaesthetics may potentiate PKC translocation and down-regulation as a result of activation of PKC *in vivo*. Halothane thus has two distinct actions on the PKC signalling pathway in nerve terminals (synaptosomes): (1) activation of endogenous PKC activity that leads to increased phosphorylation of PKC substrates[15] and (2) potentiation of phorbol ester-induced cPKC translocation and down-regulation. The interactions between general anaesthetics and PKC are therefore complex; the ultimate outcome of these interactions depends on the tissue examined, PKC isoforms present, specific anaesthetic agent, dose and duration of anaesthetic treatment and possibly the coincident activation of PKC by endogenous PKC activators.

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*British Journal of Anaesthesia* 1997; **78**: 197–200

# *In vitro* neuromuscular effects of valproic acid

A. NGUYEN AND I. RAMZAN

**Summary**

The contribution of the anticonvulsant agent, valproic acid, to the interaction between neuromuscular blockers and anticonvulsants remains unclear. Therefore, this study was undertaken to examine the acute neuromuscular effects of valproic acid and its potential for interaction with neuromuscular blocking drugs. Phrenic nerve–hemidiaphragm preparations from rats were mounted in modified Krebs buffer, maintained at 37 °C and aerated with a 5% carbon dioxide–95% oxygen gas mixture. Phrenic nerves were stimulated with 0.1 Hz supramaximal pulses of 0.2-ms duration and the elicited tension of the hemidiaphragm was recorded in seven preparations in the presence of valproic acid 100, 500 and 1000 μmol litre$^{-1}$. In another six preparations, neuromuscular transmission was blocked completely with the non-depolarizing blocker tubocurarine 3 μmol litre$^{-1}$ and the hemidiaphragm muscle was stimulated directly (2 Hz and 2 ms duration). The effect of the anticholinesterase drug, neostigmine, on an established block induced by valproic acid 1000 μmol litre$^{-1}$ was also evaluated in five phrenic nerve stimulated preparations. The effect of valproic acid 100, 500 or 1000 μmol litre$^{-1}$ on suxamethonium- or atracurium-induced neuromuscular block was also evaluated. Valproic acid produced a mean of 29.7 (SEM 1.7) % and 24.7 (1.7) % block of indirectly or directly elicited muscle twitches. The concentration of valproic acid that caused half maximal paralysis did not differ between indirect (460 (59) μmol litre$^{-1}$) and direct (329 (35) μmol litre$^{-1}$) stimulation. Neostigmine 1–3 μmol litre$^{-1}$ failed to significantly alter the block of 19.8% induced by valproic acid 1000 μmol litre$^{-1}$. Valproic acid 100, 500 or 1000 μmol litre$^{-1}$ did not alter the concentrations of suxamethonium or atracurium needed to produce paralysis. These findings suggest that valproic acid does not produce significant block at the rat neuromuscular junction. The partial block that is produced is caused predominantly by a direct inhibitory effect on the muscle itself. (*Br. J. Anaesth.* 1997; **78**: 197–200)

**Key words**

Anticonvulsants, valproic acid. Neuromuscular block, atracurium. Neuromuscular block, suxamethonium. Neuromuscular block, interaction. Rat.

Anticonvulsant drugs, given either acutely or chronically, have been observed both clinically and experimentally to alter the paralysis induced by neuromuscular blocking agents. In patients receiving chronic therapy with phenytoin, resistance, as reflected by increased dose requirements and rapid recovery, has been observed to neuromuscular block induced by the non-depolarizing blocking agents pancuronium,[1] pipecuronium,[2] dimethyltubocurarine,[3 4] doxacurium,[5] rocuronium[6] and vecuronium.[7 8] Similar resistance towards pancuronium,[9] pipecuronium,[2] doxacurium[5] and vecuronium[10] has also been noted in patients receiving carbamazepine chronically. This resistance to neuromuscular blocking drugs is more pronounced when patients receive more than one anticonvulsant agent. Thus resistance to atracurium-induced block in patients with intractable seizure disorders was more pronounced when patients received carbamazepine chronically with either phenytoin or valproic acid compared with carbamazepine alone.[11] Similar additive effects during chronic combination therapy with anticonvulsants have been observed in patients with the non-depolarizing agents doxacurium[5] and pipecuronium[2].

In contrast, acute anticonvulsant use has been shown to potentiate the paralysis induced by neuromuscular blocking agents. Thus an acute 10 mg kg$^{-1}$ i.v. dose of phenytoin potentiated established neuromuscular paralysis induced by vecuronium in neurosurgical patients.[12] This effect was confirmed in another study where the neuromuscular blocking dose of vecuronium was reduced substantially in patients receiving phenytoin acutely.[13] Carbamazepine 10 mg kg$^{-1}$ i.v., administered acutely, potentiated the paralysis induced by either suxamethonium or atracurium in rats.[14] However, there is no information on other anticonvulsants, including valproic acid, administered acutely, either alone or in combination with phenytoin or carbamazepine.

Valproic acid, a broad spectrum anticonvulsant, is used widely, either alone or in combination with other anticonvulsants, in the treatment of primary generalized epilepsy or partial seizures.[15] Valproic acid therefore has the potential to interact with neuromuscular blocking drugs when it is used either acutely or chronically. As no information is available on the nicotinic actions of valproic acid, this study

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was designed to examine the acute neuromuscular effects of valproic acid. Specifically, the *in vitro* neuromuscular effects of valproic acid alone and its influence on the neuromuscular blocking actions of a depolarizing blocker, suxamethonium, and a non-depolarizing agent, atracurium, were examined using the rat phrenic nerve–hemidiaphragm muscle preparation.

## Materials and methods

After approval by the University of Sydney Animal Care and Ethics Committee, triangular shaped hemidiaphragms with their attached phrenic nerves were obtained from 300–400 g male Sprague–Dawley rats. Each nerve–muscle preparation was mounted in a 50-ml organ bath containing modified mammalian Krebs solution of the following composition (mmol litre$^{-1}$): $Na^+$ 118, $K^+$ 6.2, $Ca^{2+}$ 1.4, $Mg^{2+}$ 0.9, $Cl^-$ 125.8, $H_2PO_4^-$ 1.2, $HCO_3^-$ 25 and glucose 11, maintained at 37 °C and bubbled with 5% carbon dioxide in oxygen. The phrenic nerve was stimulated supramaximally (approximately 2 V) at intervals of 0.5 s for 2 s (2 Hz) with rectangular pulses of 0.2-ms duration repeated every 10 s (train-of-four stimulation pattern). The resulting isometric muscle twitches were recorded using a Grass FT03 force displacement transducer and computerized data acquisition (MacLab) system. The first twitch response in the train (T1) was used to quantify neuromuscular block.

In the first experiment, organ bath concentration–response relationships for valproic acid alone were generated in seven nerve–muscle preparations by successive 100-μl additions of saline solutions of sodium valproate to generate organ bath concentrations of 5, 50, 100, 200, 400, 600, 800 and 1000 μmol litre$^{-1}$ of valproic acid. The preparations were exposed to each concentration for 10 min. Addition of valproic acid did not change the pH of the organ bath solution by more than 0.03 pH units. The direct effects of valproic acid on hemidiaphragm muscle itself was also studied in another six preparations by completely blocking neuromuscular transmission with tubocurarine 3 μmol litre$^{-1}$ and then supramaximally stimulating the muscle directly (5 V, 2 Hz and 2-ms duration). The concentration–response curve was then generated by adding successive amounts of valproic acid, as in the first study.

In a third study, designed to understand the mechanism(s) by which valproic acid produced its neuromuscular effect, neostigmine 1, 2 and 3 μmol litre$^{-1}$ was added to five preparations to examine its effect on established neuromuscular block induced by valproic acid 1000 μmol litre$^{-1}$. Indirect (phrenic nerve) stimulation was used to generate muscle twitches.

In the final experiment, the acute *in vitro* effects of valproic acid on neuromuscular block induced by either suxamethonium or atracurium were determined. The organ bath concentration–response relationships were generated for both suxamethonium and atracurium in the absence and presence of valproic acid 100, 500 or 1000 μmol litre$^{-1}$. Suxamethonium curves were produced in seven nerve–muscle preparations using freshly prepared saline solutions of the blocker to yield organ bath concentrations of 1–30 μmol litre$^{-1}$ while final bath concentrations of atracurium of 1–20 μmol litre$^{-1}$ were generated in six preparations using fresh saline diluted commercial injection solution. In each case, the concentration–response curves for each neuromuscular blocking agent alone was generated first, then the preparation was washed with fresh Krebs buffer until a stable baseline twitch response was re-established before the experiment was repeated with one concentration of valproic acid which was added just before the neuromuscular blocker. These interaction studies between valproic acid and suxamethonium or atracurium were undertaken with indirect (phrenic nerve) stimulation.

The organ bath concentration–response relationships for valproic acid, produced by both indirect (phrenic nerve) or direct (muscle) stimulation, were fitted to an Emax equation of the form:

$$E = E_{0} + (Emax - E_0) \times C / Cmax_{50} + C$$

where E and Emax=paralysis and maximum paralysis, respectively, $Cmax_{50}$=concentration causing 50% maximum paralysis, $E_0$=baseline paralysis which was not zero at the lowest drug concentration used, and $C$=organ bath concentration.

The pharmacodynamic variables for the neuromuscular effects of valproic acid using either indirect or direct stimulation were compared using the unpaired Student's *t* test. The neuromuscular effect of valproic acid alone or after addition of different concentrations of neostigmine were compared statistically using one-way analysis of variance (ANOVA). Suxamethonium or atracurium paralysis data in the absence or presence of valproic acid at the three concentrations (100, 500 or 1000 μmol litre$^{-1}$) were also fitted to the sigmoid Emax (Hill) equations mentioned previously, except that Emax was set to 100% and thus $Cmax_{50}$ represented the neuromuscular blocker concentration corresponding to 50% paralysis. All fittings were carried out using a personal computer based iterative procedure (PCNONLIN). Pharmacodynamic variables for the two neuromuscular blockers with or without valproic acid, respectively, were compared statistically using the paired Student's *t* test. Statistical significance was defined at $P<0.05$. All data are expressed as mean (SEM).

## Results

Using indirect (phrenic nerve) stimulation, valproic acid alone, in the concentration range 5–1000 μmol litre$^{-1}$, produced partial neuromuscular block of 29.7 (SEM 1.7) %, with a half-maximal concentration of approximately 450 μmol litre$^{-1}$. Direct muscle stimulation after complete block of neuromuscular transmission with tubocurarine produced a similar (24.7 (1.7) %) degree of block over the same valproic acid concentration range (table 1). Thus the concentration–response curves for valproic acid using either phrenic nerve or direct hemidiaphragm muscle stimulation were similar and superimposable (fig. 1).

*Table 1* Mean (SEM) maximum paralysis (Emax) and concentration causing half maximal paralysis (Cmax$_{50}$) for the neuromuscular blocking action of valproic acid using either indirect (phrenic nerve) or direct (muscle) stimulation. No significant differences

| Stimulation mode | $n$ | Emax (%) | Cmax$_{50}$) (μmol litre$^{-1}$) |
|---|---|---|---|
| Indirect | 7 | 29.7 (1.7) | 460 (59) |
| Direct | 6 | 24.7 (1.7) | 329 (35) |

*Table 2* Mean (SEM) Cmax$_{50}$ values for suxamethonium and atracurium in the absence or presence of various concentrations of valproic acid. No significant differences

| Valproic acid (μmol litre$^{-1}$) | $n$ | Suxamethonium (μmol litre$^{-1}$) | $n$ | Atracurium (μmol litre$^{-1}$) |
|---|---|---|---|---|
| Control | 7 | 7.8 (1.0) | 6 | 8.3 (0.9) |
| 100 | 7 | 8.2 (0.9) | 6 | 9.0 (0.7) |
| Control | 7 | 7.7 (0.6) | 6 | 7.2 (0.2) |
| 500 | 7 | 7.9 (0.7) | 6 | 8.0 (0.8) |
| Control | 7 | 7.3 (1.3) | 6 | 8.5 (0.2) |
| 1000 | 7 | 6.5 (0.6) | 6 | 8.9 (0.3) |

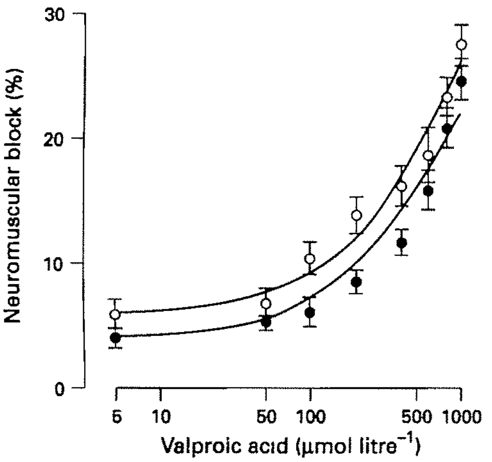

*Figure 1* Dose–response curves for valproic acid-induced neuromuscular block using indirect, phrenic nerve (○) or direct, hemidiaphragm muscle (●) stimulation. Data are mean, SEM, together with the predicted relationships ($n$=7 or 6, respectively).

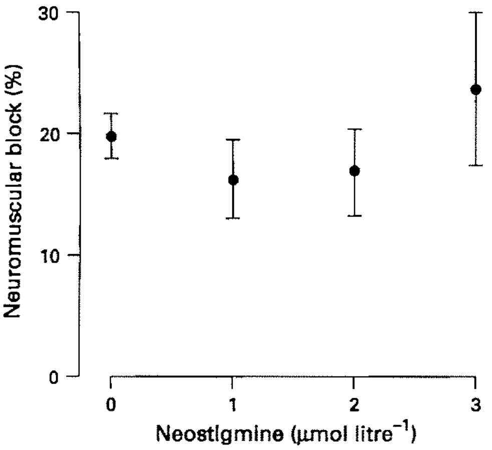

*Figure 2* Effect of the anticholinesterase, neostigmine, on neuromuscular block elicited by valproic acid 1000 μmol litre$^{-1}$ during indirect (phrenic nerve) stimulation. Mean, SEM ($n$=5). Neuromuscular block induced by valproic acid was not significantly altered after exposure to any concentration of neostigmine.

Neostigmine 1–3 μmol litre$^{-1}$ decreased neuromuscular block induced by valproic acid only transiently. Statistical analysis revealed that none of the three concentrations of neostigmine significantly reversed the paralysis induced by valproic acid (fig. 2).

Valproic acid 100, 500 or 1000 μmol litre$^{-1}$ when used with suxamethonium or atracurium failed to alter the concentration–response curve for either neuromuscular blocker. Thus the concentration of each blocker eliciting 50% block was the same in the absence or presence of valproic acid (table 2).

## Discussion

We have demonstrated that the anticonvulsant agent valproic acid exerted only a small neuromuscular blocking effect in the phrenic neve–hemidiaphragm preparation of the rat. At normal clinical doses (30–60 mg kg$^{-1}$) which yield concentrations in the range 200–700 μmol litre$^{-1}$, neuromuscular block was only 15–20%. Even at the highest concentration (1000 μmol litre$^{-1}$) only partial (29.7%) block was observed. Thus valproic acid, unlike the anticonvulsant phenytoin, is unlikely to depress neuromuscular function or potentiate neuromuscular blocking agents when surgical patients receive valproic acid acutely either before or during neurosurgical procedures. The small neuromuscular effect noted with valproic acid appears to be caused by a direct inhibitory effect at the muscle or postsynaptic effects. This is reflected in similar neuromuscular dose–response curves when the preparations were stimulated either indirectly via the nerve or directly via the muscle. Thus the predominant effect of valproic acid seems to be at the level of the muscle itself, where it appears to reduce muscle sensitivity. This postulated mechanism is also consistent with the lack of an effect of the anticholinesterase, neostigmine, on neuromuscular block elicited by valproic acid. If valproic acid was producing its effect via a depolarizing mechanism, then neostigmine would deepen the valproic acid-induced block. In contrast, if a non-depolarizing effect was being produced by valproic acid, then reversal of paralysis would have been observed. No such effects were observed when neostigmine was tested in the phrenic nerve–hemidiaphragm preparation.

That valproic acid was not producing its small neuromuscular effect via either a depolarizing or non-depolarizing mechanism is supported further by the results of interaction studies with suxamethonium and atracurium. Thus despite the use of higher than therapeutic concentrations of valproic acid, there were no alterations in the concentration–response curve for either suxamethonium or atracurium. This also indicates an alternative mechanism for the neuromuscular effect of valproic acid.

Previous *in vitro* rat experiments have shown that several other anticonvulsants, including phenytoin, trimethadione, phenobarbitone and ethosuximide produced neuromuscular block at the rat neuromuscular junction.[16] Similar results have been obtained with these agents at the frog neuromuscular junction.[17] No previous studies, however, either in patients, at the rat neuromuscular junction or in other species, have examined the neuromuscular effects of valproic acid.

The acute neuromuscular effects of valproic acid demonstrated in this study are opposite to the effects noted with chronic use of anticonvulsant drugs, including valproic acid. The chronic effects are more likely to result from enzymatic metabolism of neuromuscular blockers resulting from enzyme induction after chronic exposure to anticonvulsants. The acute neuromuscular effects of valproic acid, as observed in this study, reflect the directs effects of this anticonvulsant agent at the neuromuscular junction itself.

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REVIEW ARTICLE

# Cytokines in anaesthesia

P. SHEERAN AND G. M. HALL

Cytokines are a heterogeneous group of proteins, variously termed lymphokines, monokines, interleukines and interferons, which act on cell surface receptors to regulate and modify cell growth, maturation and repair. In addition to their longer-term effects on cell growth and differentiation, cell-mediated host–defence mechanisms and chronic diseases such as rheumatoid arthritis, cytokines also mediate several acute effects such as the inflammatory response. Cytokines are produced from activated leucocytes, in particular monocytes, and also from activated fibroblasts and endothelial cells.[12] Activation of these cells is one of the earliest cellular responses to tissue injury and is associated with release of a variety of inflammatory mediators, including cytokines, arachidonic acid metabolites, complement split products, lysosomal enzymes and oxygen-free radicals. Cytokines derived from mononuclear phagocytes mediate non-specific immune responses and some parts of the metabolic response to injury.[11] They have local and systemic effects, both mediated by activation of specific receptors. The other principal stimulus to the metabolic response to injury is afferent neuronal input from the injured or operative site.

This review is confined to activation of the cytokine network and the acute phase response found in surgery and trauma. Chronic stimulation of cytokine secretion, for example in sepsis, has been discussed recently.[18]

## Discovery of cytokines

Early studies of cytokines from 1950 to 1970 involved the description of numerous protein factors produced by different cells that mediated particular functions *in vitro*. Evidence implicated thymus-derived T lymphocytes as the cells which interacted specifically with antigen to release these protein factors, which were termed lymphokines to show their origin and function. Simple cell culture supernatants influenced the behaviour of target cells in many ways, indicating that cellular immune functions were regulated by soluble factors. It was at this time that antiviral interferons, fever-producing pyrogens and macrophage-activating factor were discovered.

The second phase of cytokine research involved the purification and characterization of many individual cytokines. It was realized that diverse effects were often mediated by the same peptide, and that cytokines were synthesized principally by leucocytes to act primarily on other leucocytes and thus were termed interleukins. However, preparations of cytokines at this time were often impure and many of the cytokine antibodies available were not specific. This hampered identification of, and distinction between, various cytokines.

In the past decade, molecular cloning and the production of highly specific, neutralizing antibodies, have resulted in the precise identification of the structure and properties of individual cytokines. All cytokines interact with specific receptors and it is the elucidation of the structure of these receptors and the signalling pathways used that are beginning to provide mechanisms and explanations for the often bewildering and diverse biological effects of this group of molecules.[66]

## Characteristics of cytokines (modified from Molloy, Mannick and Rodrick[86] and Abbas, Lichtman and Pober[1])

Cytokines have the following properties:

(1) They are low molecular weight (<80 kDa) secreted proteins, often glycosylated.

(2) They are involved in immunity and inflammation where they regulate the amplitude and duration of response. Cytokine secretion is a brief, self-limiting event.

(3) Cytokines are extremely potent, generally acting at picomolar concentrations.

(4) Cytokines, in common with other polypeptide hormones, initiate their action by binding to specific receptors on the surface of the target cell. Cytokines tend to be paracrine (act on a nearby cell) or autocrine (act on the same cell), rather than endocrine (secreted into the circulation to act on a distant cell).

(5) Activation of surface receptors leads ultimately to a change in the pattern of cellular RNA and protein synthesis, and to altered cell behaviour.

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(6) Cytokines act on many different cell types—pleiotropism.

(7) Cytokines often influence the synthesis and action of other cytokines.

(8) Cytokines often have multiple effects on the same cell.

(9) Cytokines act as regulators of cell division for many target cells, that is as growth factors.

(10) The response of a cell to a given cytokine is dependent on the local concentration of the cytokine, cell type and other cell regulators to which it is concomitantly exposed.

Most cytokines are synthesized as they are required and are not stored. However, some cytokines are presynthesized and stored in cytoplasmic granules. For example transforming growth factor-beta1 (TGF-β1) is stored in alpha granules of platelets and released when stimulated by thrombin.[9] Other instances of cytokines stored in this way include tumour necrosis factor-α (TNF-α) in some mast cells,[56] granulocyte/macrophage colony stimulating factor (GM-CSF), platelet factor 4 (PF-4) and platelet derived growth factor (PDGF).[69] Presynthesized cytokines can also be stored as membrane proteins, for example TNF-α, interleukin 1β (IL-1β), endothelial growth factor (EGF) and transforming growth factor α (TGF-α)[78] or form complexes with cell surface binding proteins or extracellular matrix, for example transforming growth factor β (TGF-β), macrophage inflammatory protein 1β (MIP-1β) and interleukin-8 (IL-8).[101 133] This serves as an immediate source of cytokine when the tissue matrix is broken down during injury and repair.

## Role of cytokines in the immune response

The immune response is divided into the non-specific (or innate) and specific (or acquired) immune response. Non-specific defence includes physical barriers, several phagocytic cells and various blood-borne molecules. This defence mechanism is present before exposure to foreign macromolecules. It is not enhanced by exposure and it does not discriminate between foreign substances.

In contrast, the specific immune response is induced by exposure to foreign macromolecules. It is specific for each macromolecule and increases in magnitude with each successive exposure. In essence, the specific immune response serves to enhance the non-specific immune response.

### NON-SPECIFIC IMMUNITY

When a foreign substance enters the body, the initial attempts to eliminate it come from an inflammatory response led by neutrophils and macrophages. In engulfing the foreign molecules, some of these cells extrude foreign antigen onto the cell surface, so becoming antigen presenting cells (APC). They are involved in the initial stages of specific immunity and also synthesize and release cytokines. Other active products of these cells are proteolytic enzymes and reactive oxygen species.

In conjunction with other cells of the immune system, such as natural killer (NK) cells and T helper lymphocytes (see below), macrophage activation is critically dependent on cytokine production. The complement system also plays a supportive role in the non-specific immune response. These proteins are synthesized in the liver and, when activated, augment phagocytosis and can cause direct cytolysis.

Other cells involved in this non-specific first line of defence are NK cells and lymphokine-activated cells (LAK cells). NK cells are large granular lymphocytes that destroy cells by direct contact, in a non-major histocompatibility complex-dependent manner. They can be regarded as cytotoxic lymphocytes (CTL) or CD8+ lymphocytes, without a T cell receptor for antigen, that is they have not resulted from overt antigenic stimulation. These cells were previously termed null cells, as they did not express markers for either T or B cells. While much is still not known about this group of lymphocytes, they kill their target cells by mechanisms similar to the CTL.

The major histocompatibility complex (MHC) is a region of polymorphic genes expressed on the short arm of chromosome 6, whose products (termed MHC-encoded proteins or MHC antigens) are expressed on the surfaces of a variety of cells.[87 97] Thus the NK cell response, by acting in a non-MHC-dependent manner, is not antigen-dependent. NK cells also release TNF and interferons. In response to IL-2 and IL-12, NK cells are a potent source of interferon-γ (IFN-γ); in T cell deficient mice, IFN-γ from NK cells activates macrophages to provide a cellular response. LAK cells are formed when NK cells are exposed to high concentrations of IL-2 or interferon-α (IFN-α). They attack a broader range of target cells than NK cells, again in a non-specific manner. NK cells act in the initial response to a foreign antigen, attempting to eradicate the infected cell before the appearance of specific cytotoxic lymphocytes. If the stimulus is large enough, as in graft *vs* host reactions, NK cells differentiate into LAK cells, which, in common with other activated cells release cytokines to maintain the response.

### SPECIFIC IMMUNITY

Specific immune responses occur after exposure to antigens, through a chain of events that results in highly specific antibodies (humoral immunity) or production of a specific set of lymphocytes (cell-mediated immunity).

The antigen receptors of B lymphocytes (bursa or bone-marrow derived lymphocytes) are membrane-bound forms of antibodies. Antigen binds to these membrane-bound antibody molecules to initiate the sequence of B cell activation, which culminates in the production of effector cells that actively secrete antibody molecules (humoral immunity).

T lymphocytes play a central role in specific immune responses to protein antigens. T lymphocytes can recognize and respond to foreign antigen only when it is presented in a complex with a self MHC molecule, on the surface of an appropriate APC cell. There are two different types of MHC molecule, class I and class II. Any given T lymphocyte can only recognize foreign antigen bound to either a class I or class II MHC molecule.

Two types of T lymphocytes occur, T helper cells and cytolytic T cells. They can be differentiated from each other because they express different membrane proteins. These different membrane proteins can be recognized by antibodies, or more specifically a "cluster" of monoclonal antibodies. These membrane proteins are termed CD molecules or "cluster of differentiation" molecules. Most helper T cells express a surface protein termed CD4, and most cytolytic T lymphocytes express a different marker termed CD8. Apart from the invaluable role the CD antigens play in identifying, isolating and analysing the specificities of different lymphocyte subsets, CD antigens are also important in promoting cell–cell interactions and adhesion, and in transducing signals leading to lymphocyte activation.

Peptide fragments derived from extracellular protein (exogenous antigens), following phagocytosis, are expressed on the cell surface bound to class II MHC molecules and are recognized by CD4+ T cells (+ denotes activated cell). These CD4+ T cells are usually T helper lymphocytes. In contrast, peptides derived from proteins synthesized in the cell (endogenous antigens) from foreign genetic protein (viral), generally are expressed with class I MHC molecules. These are recognized by CD8+ T cells, which are usually cytolytic T lymphocytes. Therefore, whether an antigen is endogenous or exogenous determines the type of specific immune response.

There is a subset of T cells that may also inhibit immune responses, termed suppressor T cells. A major problem in the study of this group of lymphocytes has been inability to purify these cells in adequate numbers to analyse their response patterns and functions. Consequently, even basic questions remain unresolved. It seems the inhibitory effects of these suppressor lymphocytes may be mediated by suppressor proteins which are soluble receptors belonging to this lymphocyte subset, hence their antigenic specificity. What is clear is that some antigens can stimulate a group of lymphocytes whose principal role is one of down-regulation of major immune responses.

The T helper lymphocyte (Th cell) responds to the antigen on the surface of the APC. When activated, Th lymphocytes produce cytokines, which increase the number of cytokine receptors on cell membranes, resulting in further development of these T lymphocytes. Cytokines control the subsequent direction and development of T helper subsets, namely Th1 subset and Th2 subset, with each subset secreting discrete cytokine profiles. Thus bacterial stimuli activate cells of the non-specific immune system to produce IFN-γ, IL-2 and IL-12 and to drive Th1 development and cell-mediated immunity. Conversely, production of IL-4 early in the response favours Th2 development and an allergic/humoral immune response.[102]

Development of the appropriate Th subset is important because some pathogens are controlled most effectively by either a predominantly cell-mediated (Th1) or an allergic or antibody-mediated humoral immunity (Th2) type response.[102] Maturation of the T helper subsets is cytokine dependent, Th1 is dependent on IFN-γ production, which is induced by IL-12, and predominantly produces further IFN-γ and IL-2. Th2 lymphocyte development is dependent on early IL-4 production and, on activation, produces IL-4, IL-5, IL-10 and IL-13, and little or no IFN-γ.

The concept of Th1 cytokines (IFN-γ, IL-2) stimulating Th1 lymphocyte development and suppressing Th2 lymphocyte activity, and Th2 cytokines (IL-4, IL-10, IL-13) stimulating Th2 development and IgE production and suppressing Th1 lymphocyte and IFN-γ activity may be one mechanism for "suppressor T cell" activity. Transforming growth factor-β (TGF-β), an inhibitory cytokine, is a powerful inhibitor of T and B cell proliferation, and any cell that produces excess amounts of this cytokine can play a role in suppressor T cell activity.

Thus cytokines play a major role in promoting or limiting Th1 or Th2 development, and also in initiating specific immune responses to various pathogens.

### CELL ADHESION MOLECULES (CAM)

Together with the cytokines, CAM function as the molecular mechanism by which cells of the immune system communicate with each other, and appear on the surfaces of neutrophils and endothelial cells very early in an inflammatory response.[126] Cell adhesion molecules are cell surface proteins involved in the binding of cells either to each other, to endothelium or to the extracellular matrix. They attract infiltrating phagocytic cells to the site of injury, in conjunction with release of chemoattractant agents (e.g. IL-8 and monocyte chemoattractant protein-1, MCP-1). Cell adhesion molecules primarily determine the migration route of cells, although they have other functions. Increased values of CAM may represent an earlier indicator of an activated immune response than an increase in cytokine secretion. The main groups of cell adhesion molecules are the selectins and immunoglobulin superfamily (IGSF). Selectins such as endothelial leucocyte adhesion molecule-1 (ELAM-1) act in the initial phases of cell adhesion to capture leucocytes from the circulation onto the vascular endothelium. This is only a transient interaction unless other adhesion pathways are activated.

IGSF adhesins include intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). These are ligands for β1 and β2 integrins. This combination of ligand–integrin pairs is involved in establishing firm adhesion after the initial selectin-mediated adhesion. These pairs are also involved in the transfer of cells across endothelium to sites of inflammation.

## Classification of cytokines

The principal biological actions of a particular cytokine fall into four broad categories, although many cytokines may function in more than one of these categories:

### (A) MEDIATORS OF NATURAL IMMUNITY

This group includes those cytokines that protect against viral infection and those responsible for the protective inflammatory response against bacteria, such as TNF-α, IL-1, IL-6 (minor role) and the chemokines (cytokines whose principal effect is one of chemotaxis of leucocytes). Also included in this group are IL-5 (responsible for eosinophil chemotaxis) and IL-8 (responsible for neutrophil chemotaxis). Chemokines can be regarded as a distinct class of cytokine, in their own right.

### (B) REGULATION OF LYMPHOCYTE ACTIVATION, GROWTH AND DIFFERENTIATION

Some cytokines are involved in the development of specific subsets of lymphocytes. The subset determines the type of immune response, namely IL-2 preferentially favours Th1 lymphocyte development and a cell-mediated immune response; IL-4 favours Th2 lymphocyte development and an allergic response (IgE production, mast cell development and adhesion molecule production responsible for eosinophil and basophil chemotaxis). TGF-β is an "anti-cytokine", in that it largely counteracts the effects of the proinflammatory cytokines. It is included in this group of cytokines because it antagonizes many lymphocyte responses such as CTL maturation and activation of macrophages.

These cytokines are secreted in response to antigen recognition by lymphocytes, mediating the activation phases of specific immune responses. Most of the cytokines are produced by T cells, especially antigen-specific CD4+ T lymphocytes. Other examples include IL-1, IL-6, IL-12, IL-7, IL-9 and TNF.

### (C) REGULATORS OF IMMUNE-MEDIATED INFLAMMATION

These cytokines activate non-specific inflammatory cells in response to specific antigen recognition by T lymphocytes. IFN-γ activates macrophages to phagocytose microbes and, with other cytokines regarded as macrophage activating factors (MAF), can also kill tumour cells. IFN-γ is the principal MAF, others include GM-CSF, and to a lesser extent IL-1 and TNF. IFN-γ also stimulates the cytolytic activity of NK cells, activates vascular endothelium and promotes Th1 development. Other cytokines included in this group are the "pro-inflammatory" cytokines IL-1 and TNF and the "anti-inflammatory" cytokines TGF-β, IL-4 and IL-10.

### (D) STIMULATORS OF IMMATURE LEUCOCYTE GROWTH AND DIFFERENTIATION

This group includes cytokines already classified in some of the above groups; IL1, IL-3, IL-5 and IL-6. Immune and inflammatory reactions, which consume leucocytes, also elicit production of new leucocytes to replace inflammatory cells. These cytokines are collectively termed colony-stimulating factors (CSF), and specifically include granulocyte colony-stimulating factor (G-CSF), macrophage colony-stimulating factor (M-CSF) and granulocyte/macrophage colony-stimulating factor (GM-CSF).

## Cytokines relevant to anaesthesia

Cytokines play a central role in the acute inflammatory response initiated by trauma or infection. IL-1, TNF-α and IL-6 have local and systemic effects, which attempt to limit injury and the spread of infection, and provide a suitable environment for tissue healing and repair. Local effects include migration of neutrophils, lymphocytes and monocytes into inflamed areas as a result of increased permeability of the endothelium, adhesion molecules and chemotactic cytokines (chemokines) such as IL-8. Systemic changes include neutrophilia, fever production, adrenocorticotrophic hormone release, a decline in circulating zinc and iron, and synthesis of acute phase proteins by the liver. These are all components of the acute phase response, a homeostatic response to major physiological insults such as trauma, infection or surgery.

There are numerous stimuli inducing release of TNF-α and IL-1; the most potent stimulus is the lipopolysaccharide or LPS component of endotoxin. Cytokines also induce further cytokine production, for example both IL-1 and TNF-α are potent inducers of IL-6, with IL-1 30 times more potent than TNF.

The physiology of each cytokine is outlined below.

### TUMOUR NECROSIS FACTOR (TNF)

TNF is secreted as a pro-hormone and cleavage results in a 157 amino acid polypeptide.[86] In common with all cytokines, interaction with a specific receptor is necessary for a biological response. Its potency is such that occupancy of as little as 5% of its receptors produces a biochemical response.[136] It exists as two distinct polypeptides, TNF-α and TNF-β, which are antigenically different, yet bind to the same receptors and produce similar, but not identical effects. It shares a central role with IL-1 in initiating the cascade of inflammatory mediators, cytokines, complement, and activation of leucocytes, lymphocytes and macrophages that make up the immune response. Overproduction of TNF production can be disastrous to the host and is seen in such pathological conditions as cachexia,[17] autoimmune disorders[109] and meningococcal septicaemia.[54 141]

The two TNF proteins produce a diversity of effects because of (i) the ubiquity of their receptors, (ii) their ability to activate multiple signal transduction pathways and (iii) their ability to induce, or suppress, the expression of a vast number of genes coding for growth factors, cytokines, transcription factors, receptors, inflammatory mediators and acute phase proteins.[140]

Just as there are two forms of TNF, α and β, so there are two forms of TNF receptor, TNFR-I and TNFR-II (see below). Both receptor types show equally high affinity binding for either TNF-α or

TNF-β. There is also present in serum soluble TNF binding proteins that are in essence TNF receptors not bound to cell membranes. These soluble receptors compete with the bound TNF receptors for TNF and therefore limit the activity of the cytokine.[54 108]

### INTERLEUKIN-1 (IL-1)

IL-1 was known by several names until amino acid sequencing revealed a closely related family of polypeptides. IL-1 exists in two forms, IL-1α and IL-1β, that are produced from two separate genes, yet activate the same receptors with equal affinity.

IL-1 has more inflammatory and immunoenhancing potential than TNF. It stimulates myelopoesis directly, and also indirectly via several myelopoeitic growth factors, including GM-CSF. It is an endogenous pyrogen, increasing synthesis of prostaglandin $E_2$ ($PGE_2$) in the anterior hypothalamus and is involved in the development of anorexia.[86]

In common with TNF, the main stimulus for IL-1 release is LPS, endotoxin antigen. Indeed, both TNF and IL-1 share many functions and nearly all of the activities of TNF and IL-1 are enhanced when they are administered together.[39] IL-1 and TNF have a wide variety of biological activities and play an important role in stimulating T and B cells, in addition to macrophages. TNF is chemotactic for polymorphonuclear leucocytes and activates respiratory burst and degranulation of these cells releasing oxygen-derived free radicals, whereas IL-1 does not. Both have antigenic activity, causing release of prostaglandins, IL-6 and IL-8 from monocytes, and stimulate endothelial cells to produce prostaglandins, IL-6 and tissue factor III, which may play a role in disseminated intravascular coagulation. TNF and IL-1 can elicit production of tissue factor by endothelium and monocytes, down-regulating expression of thrombomodulin simultaneously. Therefore, an inflammatory reaction shifts the haemostatic balance towards coagulation and away from anticoagulation.[41]

IL-1 mediates its activities through receptors on the cell membrane, either IL-1R type I or IL-1R type II. They show 25% structural homology, and in general IL-1α binds to IL-1R type I and IL-1β binds to IL-1R type II.

It has been shown recently that all the biological effects of IL-1 can be attributed to the receptor IL-1R type I transducing a signal. The function of the IL-1R type II receptor is unknown, but it may serve as a precursor for the soluble receptor form, thus antagonizing and regulating the activity of IL-1.[112 128]

### INTERLEUKIN-6 (IL-6)

Together with TNF and IL-1, IL-6 is one of the mediators of the acute phase response. In addition to its role in the inflammatory response, it plays an important part in host defence, immune responses and haematopoiesis. Over-expression or chronic activation of IL-6 is implicated in diseases such as systemic lupus erythematosus and rheumatoid arthritis. IL-6 is expressed by several normal and transformed cell types and its production is up-regulated by numerous signals, including mitogenic and antigenic stimulation, lipopolysaccharide (LPS), IL-1, IL-2, TNF, interferon, platelet derived growth factor (PDGF) and viruses.

IL-6 exerts its activity through binding to a high affinity receptor complex comprising an 80-kDa receptor protein (IL-6R) and a 130-kDa signal transducing glycoprotein (gp-130).[61] IL-6 binds to the receptor IL-6R with only low affinity. In the presence of gp-130, IL-6 binds to the receptor IL-6R with high affinity, resulting in signal transduction. In the absence of IL-6R, IL-6 does not bind to gp-130; however, in the absence of IL-6R and the presence of soluble IL-6 receptor (sIL-6R), high affinity binding with gp-130 occurs and signal transduction is triggered. This is in direct contrast to binding between TNF and the soluble TNFR, where the complex renders TNF inactive.

The regulation and physiological significance of this soluble IL-6R and its binding with IL-6 are poorly understood, but significantly increased serum concentrations of this protein have been found in some pathological states, such as multiple myeloma, adult T cell leukaemia and HIV infection. Soluble glycoprotein 130 has also been identified in serum and it is probable that this soluble protein regulates production of IL-6.[95]

### INTERLEUKIN-2 (IL-2)

IL-2 is the major autocrine and paracrine growth factor for T lymphocytes and the quantity of IL-2 synthesized determines the size of the T cell-dependent immune response. IL-2 also stimulates production of other T cell-derived cytokines, IFN-γ and TNF-α. IL-2 and IFN-γ encourage the development of the cytotoxic Th1 subset of T lymphocytes and are responsible for cell-mediated immunity. After injury $PGE_2$ is produced by inhibitory monocytes and results in down-regulation of IL-2 synthesis.[23] It is this decrease in IL-2 production that is the most striking abnormality that has been observed in trauma-induced immunodeficiency.[44] IL-2 also augments the function of neutrophils and macrophages, stimulates growth and cytolytic function of NK cells, and is a growth factor for B cells.

The biological activities of IL-2 are mediated by binding to a multi-molecular cellular receptor, namely, IL-2Rα, IL-2Rβ and IL-2Rγ. Full details of signal transduction are not known but the IL-2Rγ receptor is common to several other cytokine receptors. As with other cytokine receptors, a soluble form of IL-2Rα exists. Its function is unclear, but it is an indication of T cell activation and may be able to predict the onset of transplant rejection.[142]

IL-2 has shown promise as an anticancer drug because it stimulates LAK cells and tumour-infiltrating lymphocytes (TIL).[117 148] High doses of IL-2 improved survival in a murine model of burns and sepsis.[57] Furthermore, low doses of IL-2 combined with indomethacin improved survival and restored normal immune response in this murine model.[65]

Antibodies to IL-2 and IL-2 receptors may have potential in the prevention of allograft rejection and suppression of auto-immune disease.

### INTERLEUKIN-3 (IL-3)

IL-3 acts as a mast cell colony-stimulating factor (CSF) and a CSF on haematopoietic cells in bone marrow. It is regarded as a multilineage colony-stimulating factor and has similar actions to GM-CSF.

### INTERLEUKIN-4 (IL-4)

IL-4 is involved, together with IL-5 and IL-13, in the differentiation of Th2 lymphocytes from immature Th (helper) lymphocytes. The main physiological function of this class of lymphocytes is the defence against helminthic infections and allergic responses. IL-4 is produced by Th2 lymphocytes and is the major cytokine involved in IgE production after B cell activation and proliferation. IL-4 stimulates expression of certain adhesion molecules (VCAM-1) on endothelial cells to aid rapid transfer of inflammatory cells, especially eosinophils to areas of inflammation. IL-4 inhibits activation of macrophages and the macrophage activating effects of IFN-γ, preventing production of Th1 cytokines, nitric oxide and prostaglandins. IL-10, another Th2 cytokine, shares these effects.

### INTERLEUKIN-5 (IL-5)

IL-5 is a very potent chemotactic agent for eosinophils and acts as a stimulator of B cells. IL-4, IL-5, Th2 lymphocytes and eosinophils are found at sites of allergic reactions and circulating values may be increased in patients prone to allergies.

### INTERLEUKIN-7 (IL-7)

IL-7 is an early growth factor of both B and T lymphocyte cell lines.

### INTERLEUKIN 8 (IL-8)

This is a potent chemotactic agent for neutrophils which together with the inflammatory cytokines have been implicated in ischaemic/reperfusion injury. Pulmonary dysfunction after cardiopulmonary bypass is common and is thought to be caused by neutrophil-mediated endothelial damage and reperfusion injury. IL-8 release correlated significantly with the duration of cardiopulmonary bypass in paediatric patients.[47]

### INTERLEUKIN 9 (IL-9)

IL-9 acts directly on T cell growth, and not merely as a cofactor for the major T cell growth factors such as IL-2, IL-4 and IL-7. It promotes mast cell growth in conjunction with IL-3

### INTERLEUKIN-10 (IL-10)

Most of the immunosuppressive effects of IL-10 result from inhibition of the activity of the antigen presenting cell (APC).[16] IL-10 profoundly suppresses activation of macrophages, inhibiting their ability to secrete cytokines and to act as accessory cells for stimulation of T cell and NK cell function. It has been described as a cytokine synthesis inhibitory factor.

IL-10 down-regulates cell-mediated responses, suppressing the production of $PGE_2$ and pro-inflammatory cytokines, IL-2 and IFN-γ.[16 98] It also enhances release of soluble TNF receptor and inhibits the expression of surface receptor/adhesion molecule ICAM-1.[146]

The Epstein–Barr virus shares similar cellular activities with IL-10 and at least two of the herpes viruses harbour analogues of the IL-10 gene. This may be important in the host–virus relationship. Induction of IL-10 synthesis during infection may be an important strategy by which micro-organisms evade cell-mediated immune destruction and improve the chances of survival. IL-10 also stimulates B cell growth and differentiation.

### INTERLEUKIN-11 (IL-11)

IL-11 has several effects on haematopoietic and non-haematopoietic cell populations. It has synergistic effects with IL-3 and IL-10 on megakaryocytes and pre-B lymphocytes.

### INTERLEUKIN-12 (IL-12)

IL-12 is an important regulator of cell-mediated immune responses because it has multiple effects on T cells and NK cells and is a powerful inducer of IFN-γ production. IL-12 is an important initiator of Th1 cell development acting either directly or indirectly via induction of IFN-γ production. In the presence of IL-4, however, these effects are overcome, favouring the production of Th2 cells. IL-12 is also the most potent stimulator of growth and development of resting, or activated, NK cells and stimulates production of IFN-γ by these cells.

### INTERLEUKIN-13 (IL-13)

This recently discovered cytokine has overlapping physiological properties with IL-4. It has 30% homology with IL-4 and has similar effects on macrophages, monocytes and B cells, but no effect on T cells.[85]

IL-13 can inhibit the production and expression of pro-inflammatory cytokines and, similar to IL-4 and IL-10, is regarded as a potent anti-inflammatory cytokine that suppresses cell-mediated immunity. IL-13 stimulates neutrophils to produce the IL-1 receptor antagonist, IL-1ra, which results in inhibition of the central inflammatory mediator IL-1.[93]

### INTERLEUKIN 14 (IL-14)

IL-14 enhances the proliferation of activated B cells and stimulates immunoglobulin synthesis.[5]

### INTERLEUKIN-15 (IL-15)

IL-15 shares many of the properties of IL-2, including stimulation of T lymphocytes. It is also responsible for *in vitro* generation of alloantigen-specific cytotoxic T cells and non-antigen specific lymphokine activated killer (LAK) cells. It is produced mostly by epithelial cells and monocytes, but is also found in a wide variety of cells.

The IL-15 receptor has the IL-2 receptor beta and gamma chains in its structure, but not the alpha chain.[55]

### INTERLEUKIN-16 (IL-16)

IL-16 has no homology with other known cytokines and was previously known as lymphocyte chemoattractant factor (LCF). It is secreted from CD8+ cells and induces a migratory response in cells expressing the CD4 molecule, namely lymphocytes, monocytes and eosinophils. It may be that IL-16 has the ability to suppress HIV replication in CD8+-depleted monocytes.

### INTERLEUKIN-17 (IL-17)

IL-17 is a protein whose receptors are expressed by a wide variety of cells. It stimulates T cells and acts in a pro-inflammatory manner by activating the transcription protein NF kappa beta, resulting in increased expression of IL-6, IL-8 and ICAM-1 by fibroblasts.

### PLATELET ACTIVATING FACTOR (PAF)

PAF is a family of compounds structurally related to acylglycerol-ether-phosphorylcholine, a membrane phospholipid. It is synthesized after activation of phospholipase $A_2$ and released from platelets, basophils, neutrophils, monocytes and macrophages.[48]

PAF is also released from vascular endothelium by TNF, IL-1 and lipopolysaccharide (LPS) and has been closely linked to the profound shock seen in anaphylaxis and endotoxaemia.[129] A correlation between high concentrations of PAF and profound shock has been shown in patients with acute pancreatitis and severe infections (gram-negative septicaemia, meningitis, malaria). In some animal models, PAF receptor antagonists offer partial protection.[60 72 127]

### INTERFERON-GAMMA (IFN-γ)

IFN-γ is produced by CD4+ and CD8+ T lymphocytes and NK cells and has potent immunoregulatory effects. In common with IFN-α and β, IFN-γ is an inhibitor of viral replication. IFN-γ influences the class of antibody produced by B cells, up-regulates class I and class II MHC antigens, and is an important initiator of the Th1 subset of lymphocytes and subsequent cell-mediated immunity. It increases the efficiency of macrophage-mediated killing of intracellular parasites. IFN-γ counteracts the effects of IL-4 and thus inhibits the activity of Th2 cells.[90]

### INTERFERON-ALPHA (IFN-α), INTERFERON-BETA (IFN-β)

While there is only one gene for IFN-γ and IFN-β, there are 15 functional genes for IFN-α. IFN-α and IFN-β are produced by most cells in response to viral infection. They have potent antiviral activity, but at higher concentrations have antiproliferative activity against both normal and tumour cells. These activities have been exploited therapeutically.

### TRANSFORMING GROWTH FACTOR ALPHA AND BETA (TGF-α AND β)

All cells have receptors for, and respond to, TGF-β. However, there is no structural or functional similarity between the two TGF molecules. Indeed, their roles may be opposed as TGF-α is a growth stimulator while TGF-β is a growth inhibitor (although it can be stimulatory for some cells of mesenchymal origin).

TGF-α is structurally similar to, and shares the same receptor as, epidermal growth factor (EGF), another important member of this large group of cytokine growth factors. EGF stimulates the basal epithelial cell layer of the skin and it can also stimulate bone resorption. The EGF receptor is a transmembrane tyrosine kinase receptor and is over-expressed in various human solid tumours and tumour-derived cell lines, suggesting it is involved in tumour progression.[78] TGF-α has an important role in promoting cell proliferation in various tissues, for example the formation and resorption of bone, and wound healing.

TGF-β is found in the highest concentrations in human platelets and bone, but is produced by many cells. The actions of TGF-β are highly pleiotropic. As a cytokine, TGF-β is important because it antagonizes many lymphocyte responses; it inhibits T cell proliferation, maturation of CTL and macrophage activation. It acts on polymorphonuclear leucocytes and endothelium to counter the effects of pro-inflammatory cytokines. TGF-β can, therefore, be regarded as an anti-cytokine, as it is a negative regulator of immune responses. *Leishmania braziliensis* over-induces TGF-β production, thereby down-regulating the host's immune response and increasing the virulence of this parasite.

Although TGF-β is essentially a growth inhibitor and may be important in preventing uncontrolled proliferation of normal cells in response to mitogenic growth factors, it plays a significant role in tissue repair and regeneration. It can accelerate wound healing by promoting production of the connective tissue components collagen and fibronectin, and is also involved in regulating bone remodelling.

## Cytokine receptors

All known cytokine receptors are transmembrane proteins. The extracellular domain binds the cytokine, thereby detecting the extracellular signal, and the intracellular domain either has enzymatic activity, binds other molecules or uses a second messenger system. Proteins also exist that are structurally similar to cytokine receptors or are able to occupy their binding sites, but are not attached to the cell membrane.

Cytokine receptors have been grouped into seven families determined either by the structure of the extracellular, presenting part of the cytokine receptor, the structure of the intracellular domain of the receptor or by the method of signal transduction. Many cytokines have differing combinations of extracellular domains that may qualify them for more than one family.

### (1) RECEPTOR ONE, THE IMMUNOGLOBULIN RECEPTOR

This group usually displays one or more extracellular immunoglobulin domains. While it principally involves the receptors for IL-1α and β, it also includes some of the sequences of the IL-6R, macrophage colony-stimulating factor (M-CSF) and platelet derived growth factor (PDGF).

There are two distinct types of receptor (type I and type II). In general, type I binds IL-1α better than IL-1β, and type II receptor binds IL-1β more strongly than IL-1α.[38] It has been suggested that the function of the membrane bound type II receptor is to serve as the precursor for a soluble IL-1 binding factor that can be shed under appropriate circumstances to antagonize and modulate IL-1 activity.[128] A naturally occurring IL-1 binding protein has been described that corresponds to the soluble external portion of the type II receptor.[131]

This is the only naturally occurring cytokine receptor antagonist identified to date. It is structurally related to both IL-1α and IL-1β, and binds to the IL-1 receptors without causing signal transduction.

### (2) RECEPTOR TWO

The second receptor to be classified represents the largest group, displaying various combinations of cytokine receptor domains, fibronectin type III (FNIII domain) and, in some cases, immunoglobulin domains.

These receptors bind cytokines that share a four α-helical strand structure, for example IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, G-CSF and GM-CSF. It was known previously as the haematopoietic receptor family.

### (3) RECEPTOR THREE, INTERFERON RECEPTOR (IFNR)

This receptor type includes the type I and type II interferon receptors. One receptor type binds IFN-α and IFN-β and the other receptor binds IFN-γ. Most of the activities attributed to IFN-γ are mediated by IFN-γ proteins, which result from IFN-γ binding to its specific receptor.[58]

### (4) RECEPTOR FOUR, NERVE GROWTH FACTOR RECEPTOR (NGFR)

This fourth group of cytokine receptors, NGFR, includes the two TNF receptors that specifically bind TNF-α and β. The extracellular domains of these two receptors show similarities and can bind with equally high affinity either TNF-α or TNF-β.[34] However, the intracellular domains of the two TNF receptors are unrelated, suggesting they transmit different signals.[10] TNF-α and β use many signal transduction pathways which may explain how only a 5% occupancy of TNF receptors elicits a response.

Several groups have identified soluble TNF-binding proteins in human serum and urine.[105 124 143] Two types of these soluble proteins have been identified; they represent truncated forms of the two TNF receptors. The soluble receptors have a concentration of approximately 1–2 ng $ml^{-1}$ in the serum and urine of healthy subjects. Concentrations vary from individual to individual but are stable over time in an individual.[3]

Increased concentrations of these soluble receptors have been found in a variety of pathological states: endotoxinaemia,[139] meningococcaemia,[54] cerebral malaria,[33] systemic lupus erythematosus,[4] HIV infection[71] and in the plasma and ascites of patients with infections and malignancies.[7 36]

The soluble receptors are probably released from cells by proteolysis but the mechanisms are not well understood.[108] There are reports of a correlation between increased circulating TNF values and soluble receptor concentrations.[108 139] The precise physiological role of the soluble TNF receptor is unknown but these receptors can bind TNF *in vitro*. Thus shedding of soluble receptors scavenges TNF not bound to cell-surface receptors, limiting the effects of TNF and localizing the inflammatory response.

### (5) RECEPTOR FIVE, G PROTEIN-COUPLED SEVEN TRANSMEMBRANE SPANNING FAMILY

The fifth type of cytokine receptor is a seven transmembrane α-helical structure displayed by the receptors of complement 5a, PAF, IL-8 and many related chemokines. This receptor is similar to the structure of the β-adrenergic receptor and rhodopsin. These receptors are coupled to GTP-binding proteins and activate kinases, phosphatases and ion channels.

Members of the chemokine family exhibit 20–50% homology in their predicted amino acid sequence and, depending on slight differences in the positions of these amino acids (a conserved four-cysteine motif), can be divided into an α- and β-subfamily.[91]

### (6) OTHER RECEPTOR TYPES

There is also a group of cytokine receptors that can be classified from their intracellular catalytic domain, tyrosine kinase. On activating this receptor, tyrosine kinase phosphorylates an intracellular transcription protein with further passage of the incoming signal. The seventh cytokine receptor family type is the complement control protein superfamily.

### (7) SOLUBLE RECEPTORS AND SOLUBLE BINDING PROTEINS

The function of soluble receptors is not clear. In some instances, when bound to the ligand, they act as an agonist (sIL-6R) and in other cases as an antagonist (sTNFR). It is important to distinguish between soluble receptors (see above for TNF) and soluble binding proteins that have similar structures to cytokines and inhibit competitively the receptor (IL-1ra). Some of these soluble proteins are non-specific. Alpha-2-macroglobulin acts as a multifunctional binding protein, transporting cytokines to distant sites, but also removing them from the circulation.

In summary, soluble receptors and the soluble binding proteins can function as agonists, antagonists or simply as transport proteins, carrying cytokines to a distant target cell.

## Signal transduction pathways

Signal transduction pathways are activated when a cytokine binds to its membrane-bound receptor. There are several different pathways for signal transduction and most involve protein phosphorylation. Some cytokine receptors have intrinsic enzyme activity (tyrosine kinase activity). Receptors with no intrinsic activity need a mechanism for linking with specific cytoplasmic proteins with enzymatic function. This is undertaken by either stimulatory or inhibitory G (GTP-binding) proteins. These molecules in turn regulate the activity of adenyl cyclase and the production of phosphokinase A, cGMP phosphodiesterase and possibly phospholipases.

### SECOND MESSENGERS SYSTEMS

These systems amplify the initial cytokine signal. Cyclic-AMP–phosphokinase A is one of the best characterized second messenger systems. The activity of this complex can be regulated by phosphokinase C, which is stimulated by cytokines binding to their receptors.[24] Other important second messengers include the phospholipases, enzymes that hydrolyse membrane phospholipids. Phospholipase $A_2$ is the key enzyme in initiating arachidonic acid metabolism and prostaglandin and leukotriene production. Phospholipase C activity results in the production of inositol triphosphate (IP3) and diacylglycerol (DAG). These molecules are important second messengers and play crucial roles in the regulation of intracellular calcium (IP3)[25] and in activating protein kinase C (DAG).[26]

Cytokines stimulating a cell may produce a rapid response or a response which is delayed for several hours or even days. At a cellular level, there is either up-regulation, down-regulation or a switching on or off of gene transcription which alters protein synthesis. One method of rapid transfer of the signal from the plasma membrane to the nucleus is by the use of inactive transcription proteins in the cytoplasm. These proteins are activated by phosphorylation and, when activated, migrate into the nucleus to produce the desired effect.

Signal transduction and gene transcription are currently areas of intense research as they offer possibilities for intervention and modulation of cytokine effects.

## Cytokines and surgery

The cytokine response to surgery involves non-specific inflammation, specific immune responses, haematopoiesis and tissue repair.

### THE ACUTE PHASE RESPONSE

The acute phase response to injury limits tissue damage, isolates and destroys the infective organism, and activates the repair processes that are necessary to return the host to normal function. Usually this response lasts only a few days. However, in cases of chronic stimulation of the inflammatory cascade, continuation of some aspects of the acute phase response may contribute to the underlying tissue damage that accompanies the disease (e.g. rheumatoid arthritis).

The acute phase response consists of:

(i) Alteration of the temperature set point in the hypothalamus and generation of a febrile response mediated through production of $PGE_2$.

(ii) Change in plasma protein composition.

(iii) Increase in the number of granulocytes in peripheral blood, initially as a result of increased release from bone marrow stores and later from increased production.

(iv) IL-1 and IL-6 stimulate adrenocorticotrophic hormone (ACTH) secretion and, consequently, production of cortisol. As corticosteroids inhibit cytokine gene expression, a negative feedback mechanism operates.

Acute phase proteins are synthesized in the liver, which increases in size during this response. These proteins are involved in non-specific/specific immunity as inflammatory mediators, scavengers and protease inhibitors, and in tissue repair. Acute phase proteins include: C reactive protein (CRP), which functions as a non-specific opsonin to augment phagocytosis of bacteria, alpha$_2$ macroglobulin and other anti-proteinases, and fibrinogen.

Over 30 proteins are involved in the acute phase response. Some can be used as useful indicators of the presence and extent of an inflammatory process, for example C-reactive protein (CRP). The rate of increase in concentration of these proteins, and their rate of decline, varies from one acute protein to another. Changes in synthesis are caused by alterations in gene transcription in response to cytokine stimulation.

During the acute phase response plasma concentrations of albumin and transferrin, the iron transport protein, decrease. These are termed the negative acute phase reactants. Most of these changes can be attributed to alterations in the rate of synthesis of these plasma proteins by hepatocytes, while some are caused by increased catabolism.

There are also marked changes in serum concentrations of trace elements. Copper values increase, associated with an increased ceruloplasmin concentration, whereas there is a transient decrease in serum zinc and a persistent decrease in serum iron concentrations. This decline is caused initially by a decrease in serum values of the respective transport proteins (transferrin for iron, and albumin and alpha$_2$ macroglobulin for zinc). This results from increased vascular permeability, which is aggravated after 6 h by reduction in binding of trace element to its protein.[94]

### *Induction of the acute phase response*

The macrophage or monocyte is usually the cell that starts the acute phase response at the site of tissue injury, by releasing a broad spectrum of mediators. These mediators, of which IL-1 and TNF-α are critical, initiate the next series of reactions. These early cytokines act both locally (on stroma cells—fibroblasts and endothelium) and distally, resulting in a secondary phase of cytokine release.[12] Interleukin-6 is released in the second wave of cytokines and is a primary effector in the production of acute phase proteins and accumulation of inflammatory cells.

Circulating IL-6 values increase after all types of major surgery; increased concentrations can be detected as early as 30 min after skin incision and become significantly increased 2–4 h after surgery. The IL-6 response to surgery reflects the extent of tissue damage[29] and is decreased when surgery is undertaken with laparoscopic techniques.[68] Patients with surgical complications have normal initial increases in circulating IL-6, but then develop a large secondary increase followed by a further increase in C-reactive protein.

IL-6, IL-1 and TNF-α have been shown *in vitro* to stimulate the release of ACTH from pituitary cells.[59] Glucocorticoids inhibit IL-6 production in human monocytes but, by up-regulating production of the IL-6 receptor on hepatocytes, increase the acute phase protein response to IL-6.[59]

IL-6, together with TNF-α and IL-1, can inhibit glutamine metabolism if incubated with human fibroblasts for 12 h. Impaired glutamine metabolism results in abnormal cell growth and consequently poor wound healing in critically ill patients.[121] IL-6 activates platelets *in vitro* and enhances agonist-induced platelet aggregation via a mechanism involving cyclo-oxygenase eicosanoid metabolism.[104] This effect may play only a small part in the overall hypercoagulable response to surgery but, in the coronary circulation, changes in platelet reactivity are temporally associated with the development of unstable angina.

It has been suggested that IL-6 may be a more sensitive indicator of the degree of myocardial damage after myocardial infarction than serial creatine kinase (CK) estimations, and an association was found between the size of the IL-6 response and cardiac morbidity.[30] High concentrations of IL-6 impair cardiac function as a result of negative inotropic effects possibly consequent on impaired entry of calcium into myocardial cells.[46] Other cytokines such as TNF-α, IL-2 and PAF also have negative inotropic effects.[53 60 132]

The effects of various anaesthetic techniques on the cytokine and acute phase responses to surgery are receiving increasing attention. Regional anaesthesia had little effect on IL-6 production after pelvic surgery,[88] but it was shown that large doses of alfentanil transiently suppressed IL-6 secretion in a similar surgical model.[28] The cortisol response to surgery is sufficient to down-regulate IL-6 production[67] and large doses of glucocorticoids have been used to decrease the IL-6 and acute phase response to major abdominal surgery.[122] Unfortunately this technique was associated with a high incidence of surgical problems such as wound dehiscence.

## CYTOKINES AND IMMUNOSUPPRESSION

Immunosuppression after major trauma results mainly from T cell dysfunction and is characterized by impaired synthesis of IL-2 and IFN-γ.[43 147] The inability to produce adequate amounts of IL-2 causes incomplete T helper cell proliferation in response to antigen stimulation, and a lack of IFN-γ results in impaired ability of monocyte antigen presentation. These two cytokines are crucial to the development of the Th1 subset of lymphocytes that are responsible for cell-mediated immunity.[99] This down-regulation of IL-2 and IFN-γ appears to be a direct consequence of PGE$_2$ production in the acute phase response.[44] Other immunosuppressants include TGF-β, IL-10 and the naturally occurring antagonists, sTNF-α and IL-1ra. TGF-β induces further production of PGE$_2$ in monocytes and in some environments may produce more cell-associated TNF-α. It also suppresses IL-2- and IL-4-dependent Th development and down-regulates the T cell receptor for IL-1.[84] McBride and colleagues have recently identified significant amounts of circulating IL-10 in patients after cardiopulmonary bypass.[80] IL-10 is produced by Th2 lymphocytes and results in the production of soluble TNF-α and IL-1 receptor antagonist.

In brief, the principal immunological deficit after trauma and major surgery is decreased cell-mediated immunity from an impaired NK cell response and Th1 lymphocyte development. This results in preferential Th2 development, probably as a result of suppression of Th1 development. Recent anaesthetic reports suggest there may be some benefit from infusing cytokines, such as interferon α and β, and IL-2, on NK cell activity.[14 77]

## CYTOKINES AND WOUND HEALING

Cytokines have profound effects on various aspects of granulomatous tissue formation and re-epithelialization, critical problems in burns patients and patients with chronic ulcers.[115] The cytokines primarily involved are TGF-β, PDGF, fibroblast growth factor (FGF), EGF, IL-6 and the proinflammatory cytokines TNF-α, IL-1α and β. The role of TGF-β in wound healing seems contradictory, as it is a potent growth inhibitor for many cell types.

However, TGF-β is usually stimulatory for cells of mesenchymal origin and inhibitory for cells of epidermal origin.[89] There are numerous links between TGF-β and the macrophage, which plays a pivotal role in directing cellular responses required for wound healing. In addition to stimulating its own gene expression, TGF-β can stimulate other growth factors, such as FGF and PDGF. TGF-β is also chemotactic for monocytes and fibroblasts, encouraging their passage into the wound site, and has been shown to increase the strength of wound repair in experimental animals.[92]

PDGF can influence all cells involved in soft tissue repair and is released at wound sites by platelet α granules. Further release of PDGF is continued by activated macrophages and fibroblasts. In conjunction with EGF, other peptides, such as insulin-like growth factors (IGF) help tissue repair. It has also been demonstrated that TNF-α[74] and IL-6[100] promote healing, although over-production can have a deleterious effect.[121] There is evidence that IL-6 values in wound fluid are higher than corresponding serum values,[137] although this may reflect the extent of local tissue damage. Fahey and colleagues suggest that diabetes may obtund this IL-6 response, contributing to delayed wound closure.[42]

In bypass vascular techniques, the main cause of vein graft failure in the early postoperative period is intimal hyperplasia which may be mediated by cytokine growth factors.[63]

## CYTOKINES AND THE EXTRACORPOREAL CIRCULATION

One of the most potent stimuli for leucocyte activation, and therefore cytokine production, is exposure of blood to artificial extracorporeal circuits.[21 22] In clinical practice this concerns patients undergoing renal dialysis and cardiopulmonary bypass (CPB).

There is much conflicting data on cytokines and renal failure with some groups showing an increase in circulating values and other workers finding no change.[107 123] The main stimulus to cytokine production is the dialysis procedure and not the underlying chronic renal failure. Pereira and Dinarello suggested that the variability reported may simply reflect the wide spectrum of cytokine-secreting ability in these patients, as similar variation has been noted in healthy volunteers.[107] Other factors associated with renal failure such as poor nutrition and anaemia can also affect cytokine production. There is more inhibitory activity in plasma from haemodialysis patients than plasma from patients with renal failure and normal subjects. For example, a threefold increase in IL-1ra and soluble TNF-receptor values was found in patients receiving chronic haemodialysis.[37 107]

Cardiac surgery compounds the inflammatory response triggered by the extracorporeal circulation, first by the severity of the surgery and second by the greater damage to the cells in the CPB circuit resulting from high flows and passage through the oxygenator. The cytokine response to cardiac surgery has received considerable attention and was reviewed recently.[135] In brief, the main inflammatory cytokines are IL-6 and IL-8, with only minor increases in IL-1 and TNF. The anti-inflammatory cytokine IL-10 responds rapidly to CPB,[80] and other cytokine antagonists such as IL-1ra increase significantly.[103] Cardiac surgery has a marked suppressant effect on cell-mediated immunity.[62]

Cardiopulmonary bypass results in activation of polymorphonuclear neutrophils and their adhesion to, and chemotaxis through, vascular endothelium. This may be because of expression of CD11b and CD18 on the neutrophil and endothelial cells and expression of the adhesion molecule L-selectin. IL-8 is a neutrophil chemoattractant that induces the cell adhesion molecules CD11 and CD18.[19] Reperfusion injury is a major cause of morbidity after CPB, particularly in myocardium and lung tissue. It seems that the neutrophil, through generation of oxygen-free radicals, upsets the balance between radical-generating and radical-scavenging systems, resulting in reperfusion injury. Detailed discussion of this area falls beyond this article, and is covered well in other reviews.[21 22 83]

## CYTOKINES AND COAGULATION

Cytokines do not directly participate in coagulation reactions, but they may accelerate, or decrease, the rate of specific pathways. Thus, TNF-α and IL-1 activate the procoagulating mechanisms *in vivo*, but do not alter the clotting time.[41] The endothelium has both procoagulant and anticoagulant activities and, in the quiescent state, the latter predominates to favour blood fluidity. Cytokines can alter endothelial cell function; IL-1 increases endothelial procoagulant activity while decreasing expression of thrombomodulin. Fibrinolysis is also inhibited by IL-1, with decreased tissue plasminogen activator (tPA) and enhanced plasminogen activator inhibitor-1.[15] TNF induces tissue factor, suppresses thrombomodulin,[96] depresses endothelial fibrinolytic activity[138] and increases the permeability of the endothelial monolayers.[20]

Abnormalities of the coagulation system are a common finding in inflammatory, immune and neoplastic diseases. Cytokines, forming a key link between host response and the coagulation mechanism, modulate expression of cell surface cofactors, and factors and mediators released from endothelium and monocytes.

## CYTOKINES AND THE VASCULAR ENDOTHELIUM

Features of diseases that involve large blood vessels include dysfunction of the endothelial lining, further stimulating mediators of the inflammatory response, weakening of the artery wall and narrowing of the arterial lumen. Cytokines, and other growth factors, are responsible for the expression of cell adhesion molecules and cell migration into localized areas of vessel injury. Vascular endothelial growth factor (VEGF) stimulates endothelial cells but not smooth muscle production, while platelet derived growth factor (PDGF) has no effect on endothelial cells, but stimulates smooth muscle cell production. Fibroblast growth factor stimulates both types of cell proliferation. These growth factors, sequestered in low concentrations in normal vessels, are released after injury; their action is localized by selected expression on cells and removal by the circulation.[110]

Cell adhesion molecules, notably vascular cell adhesion molecule (VCAM), encourage migration of monocytes and lymphocytes. TNF-α, IL-1 and IFN-α alter vascular permeability by interfering with the endothelial layer.[130] Changes in the contractile state of the arterial smooth muscle, in the absence of endothelium, have been shown with at least four cytokines (EGF, PDGF, TGF-α, IL-1). In addition, the IL-1 induced generation of nitric oxide may explain the hypotension seen after administration of this cytokine.[13]

## Cytokines and the nervous system

### CENTRAL NERVOUS SYSTEM

It had been thought that cytokines, usually associated with the peripheral immune response, would only selectively cross the intact blood–brain barrier. Circulating cytokines are able to stimulate those parts of the CNS outside the blood–brain barrier (circumventricular organs), resulting in a febrile response and release of corticotrophin releasing factor (CRF).[120] Overproduction of some cytokines, such as TNF-α in bacterial meningitis, may lead to tissue injury and breakdown of the blood–brain barrier.[125] It has been demonstrated that while the pro-inflammatory cytokines may not be responsible for this breakdown in integrity of the blood–brain barrier, they are able to cross the disrupted barrier. Saturable transport systems exist for IL-1 and TNF-α, but not for IL-2.

Leucocytes are able to cross the blood–brain barrier as part of an inflammatory response and secrete cytokines. Cellular elements of the CNS such as neurones, glial and endothelial cells are also able to produce cytokines. Glial cells (the microglia is the brain's macrophage) can be activated by IL-1 and TNF-α, produced by T lymphocytes that have migrated into the CNS. These glial cells, after activation, can express either class I or class II types of MHC antigen to either subset of T lymphocyte.

Not only do cytokines have central effects resulting from systemic disease, they also have important roles in acute and chronic neurological diseases. IL-1, at low concentrations, stimulates production of nerve growth factor (NGF) and fibroblast growth factor (FGF), and is neuroprotective. However, in high concentrations, it causes massive exacerbation of the primary insult. IL-1ra markedly limits the extent of damage induced by focal ischaemia or activation of *N*-methyl-D-aspartate (NMDA) receptors in such diverse conditions as stroke, meningitis, excitotoxic damage and heat stroke.[118] Cytokines influence the production and effects of neurotransmitters and are also involved in tissue repair as IL-1 and IL-6 enhance the expression of NGF, and TNF-α initiates gliosis. Cytokines also have behavioural effects, altering sleep patterns and the social response to sickness.

### CYTOKINES AND PAIN

Inflammation is a painful process and recent reviews have emphasized a role for the primary mediators of the cytokine cascade, TNF-α and IL-1β in hyperalgesia.[45 51] Hyperalgesia induced by IL-1β depends partly on induction of bradykinin-1 receptors. It is not surprising, therefore, that pharmacological block of bradykinin and cytokine activity is an area of active pain research.[111] Bicyclic imidazoles, such as tenidap, are under intensive investigation as they have been shown to modify the progress of rheumatoid arthritis by partly interfering with cytokine production.[73]

However, recently attention has been centred on nerve growth factor (NGF). NGF regulates nociception by a direct action on primary afferent fibres, with increased amounts present in inflammation, sunburn and rheumatoid arthritis, and decreased amounts in leprosy, neuropathies and in ageing. NGF modulates the production of substance P and is a key molecule in the understanding of the phenomena of allodynia and hyperalgesia.[6] An anti-NGF preparation has been developed which will help clarify the biological activity of NGF and may increase our understanding of chronic pain.

## Cytokines and pregnancy

There is increasing evidence that cytokines, in addition to the hypothalamic, pituitary and gonadal hormones, play an important part in reproductive function.[119] Several cytokines are involved in pre- and peri-implantation developments, in maternal–fetal interactions and in the initiation of parturition. Enhanced cytokine production may be partly responsible for problems developing in the antenatal period, such as preterm delivery[75] and pregnancy-induced hypertension.[76]

The development of the pre-implantation embryo is more successful and rapid in the uterus than *in vitro*. This suggests that, while the process is autonomous, it is stimulated in the uterine environment. It is likely that epidermal growth factor (EGF), insulin-like growth factors (IGF) and leukaemia inhibitory factor (LIF) are involved in embryo development.[119]

The paternal component of the fetal genome represents a challenge to the maternal immune system. Therefore, modifications to the maternal immune response, both peri-implantation and as the pregnancy develops, occur to avoid rejection of, what is in effect, a partial allograft. Cytokines are important in communication between the developing blastocyst, maternal uterine cells and infiltrating leucocytes before implantation and as the placenta develops.[113]

Cell-mediated immunity is decreased in pregnancy.[49] A relative increase in the Th2 lymphocyte population is found, characterized by enhanced production of IL-4 and IL-10 with increased immunoglobulin production and decreased Th1 activity. IL-2 and IFN-γ (Th1 cytokines) facilitate rejection of the developing allograft and represent one example of how upsetting the balance between Th1 and Th2 cytokines has implications for the clinical course of several autoimmune diseases associated with pregnancy.[49 145] In pre-eclampsia or pregnancy-induced hypertension, increased cell-mediated immunity seems to be partly responsible for an underlying chronic rejection pattern.[76]

Magnesium is used increasingly as an anti-epileptic, sedative and hypotensive agent in the treatment of severe pre-eclampsia. This element is a non-specific, down-regulator of cytokine activity, probably by antagonizing increased intracellular calcium that is an essential signal after stimulation by cytokines.[144] Thus magnesium may work, at least in part, by inhibiting the effects of excessive cytokine activity.

## Cytokines and hypersensitivity

The immune response to allergens is virtually identical to the response to parasites, with large amounts of immunoglobulin E (IgE) produced by B lymphocytes. These B lymphocytes are stimulated by Th cells which recognize antigen displayed on the surface of the antigen presenting cell (APC). These APC stimulate the production of IL-4 which causes the B cells to produce IgE and encourages further differentiation of Th helper cells into Th2 lymphocytes with production of the "allergic" cytokines IL-4, IL-5 and IL-13. In contrast, IFN-γ inhibits this pathway of Th2 cell development and encourages development of Th1 lymphocytes and their specific cytokines IL-2, IFN-γ and TNF-β.[90 116]

Atopic allergy is a genetically determined disorder, characterized by an increased ability of B lymphocytes to produce IgE antibodies to certain forms of ubiquitous allergen, present in low concentration. Essentially, the IgE produced attaches to the $F_C$ fragments of IgE receptors on the surface of mast cells. When the mast cell is next exposed to that antigen, the antigen binds to its IgE receptors, resulting in mast cell degranulation. This degranulation results in the release of vasoactive mediators, chemotactic factors and cytokines that are responsible for the allergic cascade. In addition, eosinophils are also involved, as they invariably accumulate at the sites of allergic inflammation, and the toxic products released contribute significantly to the resulting tissue damage.

Mast cells play not only a central role in immediate allergic responses, but also serve an immunoregulatory function, through production of IL-3, IL-4, IL-5, IL-6 and TNF, and chemokines such as IL-8 (neutrophil chemotaxis).[27] Specific immunotherapy can change the cytokine profiles of the allergic Th2 cells and result in either increased Th1 cells or reduced synthesis of IL-4.[126] IFN-γ stimulates Th1 lymphocyte development at the expense of IL-4 production and hence inhibits Th2 lymphocyte development and causes a decrease in circulating IgE values. In asthma, therapy with an anti-IL-5 compound has resulted in decreased airway responsiveness. IL-4 must be an attractive target for pharmacological intervention because of its role in IgE switching, development of Th2 lymphocytes and induction of eosinophilia.[134] Glucocorticoids are the most potent drugs for controlling airway inflammation, but seem to have their principal effects on inhibiting Th2-type cytokine production (on IL-5 rather than IL-4)[70] and bronchial eosinophilia.[114]

Anaphylactic reactions during anaesthesia occur more commonly in patients with an atopic history. It may be possible to predict those atopic patients at risk of a hypersensitivity response by assessing their "state of reactivity", that is circulating concentrations of IL-4, IL-5 , IL-13 and eosinophil count. Some studies have already attempted to correlate IL-4 with IgE values.[79]

TNF and platelet activating factor (PAF) are important mediators of anaphylaxis. The use of PAF antagonists to obtund the amplification of mediator release in shock has been studied in animal models, where even delayed receptor block had some benefit.[60 72 127]

Cytokines play a central role in IgE synthesis and in the further differentiation and expansion of the various cell lines involved in the allergic response. Atopy is genetically determined but, whether this is a result of increased expression of Th2-type cytokines, decreased expression of Th1-type cytokines or a combination of the two has not been fully determined. Targeting the Th2 lymphocytes and their cytokines seems a promising approach to reduce the chronic inflammatory response of allergy and asthma. In acute and massive mediator release, as occurs in anaphylaxis, specific cytokine receptor antagonism has improved outcome in animal models.

## Cytokines and transplantation

Solid organ and bone marrow allografts represent unique forms of generalized activation of the immune system because of histoincompatibility. Many of the complications of these procedures, including rejection, graft *vs* host disease (GVHD), interstitial pneumonitis, hepatic veno-occlusive disease and microangiopathy can be related to inadequately regulated cytokine production.[64 81]

Patients in the early weeks after bone marrow transplantation are at particular risk of bacterial and fungal infection, the incidence and severity of which are related to the period of neutropaenia. Cytokine growth factors such as granulocyte colony stimulating factor (G-CSF) and granulocyte/macrophage colony stimulating factor (GM-CSF) stimulate myelopoiesis. If these factors are administered during this time, the severity and duration of neutropaenia and therefore the risk of infection, are reduced.

Cytokines play a central role in the rejection response to allograft organ transplantation.[32] The rejection response can be divided into two phases, an afferent and efferent response. The afferent response leads to activation of the recipient's immune system, as a result of recognition of foreign major histocompatibility antigens (class II type MHC or alloantigens) on the surface of donor antigen presenting cells (APC) by the recipient's Th lymphocytes. These cells produce activation antigens which they express on their cell surface. One of these activation antigens has been identified as homologous to the alpha chain of the IL-2 receptor. The Th lymphocytes produce a wide range of cytokines that initiate cellular and humoral rejection mechanisms, and have been identified in the transplanted graft during rejection.[32] IL- 1, IL-2 and IFN-$\gamma$ stimulate the development of Th1 type lymphocytes expressing CD4+ antigen that recognize class II MHC molecule. Occasionally, when mismatch occurs to class I MHC antigens only, CD8+ lymphocytes, the cytotoxic lymphocytes, can act as T helper cells. IFN-$\gamma$ also up-regulates MHC antigen expression on graft tissue, resulting in increased vulnerability of the graft. IL-2 and IFN-$\gamma$ play a central role in the rejection process. The presence of one of these cytokines within the graft may be a sign of early rejection.[31]

The efferent arm of the response occurs as a later event and results in triggering of the humoral and cellular effector mechanisms of the immune response. Immune effector mechanisms involved include delayed-type hypersensitivity reactions, NK cells, LAK cells, antibody-dependent cell-mediated cytotoxicity and complement-dependent antibody-mediated cytotoxicity.

Immunosuppression has been the traditional form of cytokine down-regulation. Non-specific agents, such as glucocorticoids, cyclophosphamide, azathioprine and anti-T-cell antibodies have been used to reduce inflammation in autoimmune diseases and post-transplantation surgery. All of these agents are directed against the T cell compartment and have more general and non-selective immunosuppressive effects. The immunophilin binding drugs, such as cyclosporin and FK506, are more selective and the newer agents give excellent primary immunosuppression and also improve rescue treatments. FK506, a much more potent immunophilin binding drug than cyclosporin, is particularly promising.[52] It inhibits the production of cytotoxic lymphocytes, specifically by blocking the synthesis of IL-2, IL-3, IL-4, GM-CSF, G-CSF, TNF and IFN-$\gamma$. As improved immunosuppression reduces the graft failure from acute rejection, chronic rejection becomes more obvious. Differentiation between acute and chronic rejection is based on time rather than the mechanisms involved.

## Down-regulation of cytokines

Cytokine activity plays a fundamental role in the pathogenesis of many inflammatory diseases. Down-regulation of cytokines, or block of their effects, can occur at various sites. The principles of influencing cytokine production, or immunomodulation, will be discussed only in outline.

### *(i) Immunosuppression*

(a) Glucocorticoids have a direct impact on cell proliferation and inhibit cytokine production.

(b) Azathioprine and cyclophosphamide inhibit cell division and disrupt DNA transcription and RNA translation resulting in decreased cytokine production.

(c) Anti-T-cell antibodies have a direct effect on T lymphocytes and therefore result in decreased T cell function. Naturally occurring autoantibodies against IL-1$\alpha$, IFN-$\alpha$, IFN-$\gamma$, TNF-$\alpha$, nerve growth factor (NGF) and IL-6 have been isolated from normal individuals and patients with acute inflammatory disorders. The significance of these autoantibodies is unknown. Synthesized antibodies (monoclonal antibodies—MAbs) have been developed against cytokines and cytokine receptors. This therapy has also been used with some success against T cell surface markers and leucocyte adhesion molecules.

(d) Immunophilin binding drugs—cyclosporin, FK506. These drugs inhibit immune responses more selectively by forming complexes with cytoplasmic transcription proteins that interfere with calcium-dependent signalling pathways.[50] IL-2 production is inhibited and hence Th1 lymphocyte development blocked.

### *(ii) Blockade of signal transduction*

When TNF binds to its receptor, it activates multiple signal pathways which may be manipulated by specific enzymatic inhibitors. For example, pentoxifylline inhibits TNF production *in vitro*. It is a xanthine derivative, and acts by inhibiting phosphodiesterase resulting in increased intracellular cAMP and decreased cellular mRNA concentrations of TNF. Another important agent is ATP–magnesium chloride (ATP–$MgCl_2$). Magnesium deficiency increases circulating IL-1, IL-6 and TNF-$\alpha$ in rodents.[144] Calcium channel antagonists may also change the cytokine response. For example, diltiazem enhanced production of cytokines and maintained immune function after haemorrhage.[82]

### *(iii) Cytokine receptors and receptor antagonists*

Cytokine receptors can be targeted in several different ways:

(a) antibodies against receptor;

(b) soluble proteins binding competitively to membrane-bound receptor;

(c) development of amino acid substitution in cytokines.

The two most studied naturally occurring specific inhibitors of cytokines are IL-receptor antagonist and soluble TNF receptors. Biological responses to IL-1 can be induced by occupancy of as few as 5% of IL-1 receptors, and *in vivo* up to 100-fold excess of IL-1ra is required to inhibit 50% of IL-1 induced responses.[40] This indicates the presence of a large number of IL-1 receptors on cells compared with the number that need to be occupied to trigger a biological response.[40] As the pattern of production and regulation for IL-1 and IL-1ra is different, the exact relationship between the two cytokines remains to be established.[8]

Soluble TNF receptors represent the cleaved extracellular domains of the TNF receptors, type I and type II. Their functions are complex; they may serve as TNF inhibitors, TNF reservoirs or, in some situations, even augment TNF effects by stabilizing its tertiary structure and prolonging its action.[2]

### *(iv) Alpha$_2$-macroglobulin*

This is a non-specific, multi-functional binding protein that serves as a proteinase inhibitor, a carrier protein and a cytokine modulator. Other examples of naturally occurring non-specific inhibitors of cytokines include lipoproteins and lipids.[38]

## CYTOKINE DOWN-REGULATION OF IMMUNE FUNCTION

There are several cytokines, TGF-β, IL-10 and IL-4, whose normal function is to inhibit further cytokine development.

### *(i) Transforming growth factor B (TGF-β)*

TGF-β promotes extracellular matrix formation and stimulates some mesenchymal cells, but also inhibits the growth of a variety of normal and transformed cells, including B cell maturation and release, NK cell activity and release of cytokines by T cells.

### *(ii) IL-10*

Interleukin-10 is produced by a selected subset of Th2 cells, macrophages and B lymphocytes with the other Th2 cytokines, IL-4 and IL-5.[48] IL-10 also inhibits antigen presentation to Th1 cells, up-regulation of the MHC class II antigen and production of TNF-α, IL-1 α, IL-1 β, IL-6 and IL-8.[35] However, IL-10 up-regulates B cell proliferation, differentiation and immunoglobin synthesis. It suppresses the production of Th1 cytokines (IL-2, IL-3, IFN-γ, TNF-β and GM-CSF).

### *(iii) IL-4*

IL-4 induces production of IL-10, a cytokine inhibitory factor, as detailed above. It also increases the production of CD8+ cytotoxic cells and decreases the number of CD4+ cells, NK cells, IL-2 activated killer cells and down-regulates IFN-γ.[106]

## Summary

The scope of cytokine biology is fascinating with widespread applications anticipated in many areas of medical science. We have emphasized the fundamental roles that cytokines play in the control of normal immunological functions, defence mechanisms and normal cell growth, and how major surgery and trauma can affect these processes. It remains to be determined if morbidity and mortality may be improved after major illness and surgery by altering cytokine production and function.

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SHORT COMMUNICATIONS

# The laryngeal mask airway and the tracheal route for drug administration

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## Summary

We undertook a study to observe if a preformed curved plastic cannula, the Trachojet, could be passed blindly down a laryngeal mask airway into the trachea in 100 anaesthetized patients. Using air aspiration and a fibreoptic scope to confirm placement of the cannula, it passed into the trachea in only 27% of patients. The air aspiration technique used for detecting tracheal cannulation was 100% successful when the cannula was inserted fully. We conclude that it may not be possible to gain access to the trachea with a Trachojet for drug administration if a laryngeal mask airway is used to maintain the patient's airway. (*Br. J. Anaesth.* 1997; **78**: 220–221)

**Key words**
Equipment, masks anaesthesia. Equipment, cannulae.

The European Resuscitation Council (ERC) recommends that the tracheal route should be used for cardiac drug administration during cardiopulmonary resuscitation (CPR) if an i.v. route cannot be established. However, if a laryngeal mask airway (LMA) is used to maintain a patient's airway, tracheal access is not guaranteed, as the LMA does not pass through the vocal cords.

The Trachojet (Evans Medical, Dunstable, Bedfordshire, UK) is a plastic, anatomically curved cannula manufactured for tracheal and endobronchial administration of drugs. It has a Luer lock connector at its proximal end for attachment of a syringe and a flange to prevent its loss into the tracheal tube. There are multiple holes to produce a spray of the injectate at the distal end with guide markings at 23, 25 and 27 cm. When inserted fully into the lumen of the LMA, the Trachojet protrudes the grille of the LMA by at least 3 cm more than the longest distance previously measured between the grille and the vocal chords.[1]

The aim of this study was to investigate if the Trachojet would enter the trachea in anaesthetized patients if passed blindly into the stem of the LMA.

## Methods and results

Local hospital Ethics Committee approval was granted and informed written consent obtained from 100 patients, ASA I or II, undergoing elective surgery. Exclusion criteria were any patient not scheduled to have an LMA inserted as part of the anaesthetic technique, those with abnormal laryngeal or tracheal anatomy, or those aged less than 18 yr.

Monitoring in the anaesthetic room included ECG, pulse oximetry and automated non-invasive arterial pressure measurement. Anaesthesia was induced with propofol 2 mg $kg^{-1}$ and fentanyl 1 $\mu g$ $kg^{-1}$ i.v. When anaesthesia was of sufficient depth to obtund laryngeal reflexes, an LMA was inserted using the technique described by the manufacturer (Intavent Ltd, Tidmarsh, Berkshire, UK) with the patient's head extended on the neck. If the LMA could not be inserted on the first attempt then the procedure was repeated, with increments of propofol as necessary. Insertion was considered successful if the LMA was inserted fully and the patient's lungs could be inflated easily. Insertion was considered difficult if it took more than two attempts. The patient was then allowed to breathe spontaneously and anaesthesia was deepened with 2.5–3% isoflurane in oxygen. After at least 5 min of preoxygenation and when the patient's vital signs had stabilized, fresh gas flow was disconnected. A Trachojet was then passed down the lumen of the LMA as far as possible with the patient's head still extended. Tracheal placement was noted by aspiration of air, as described by Wee[2], with a syringe attached to the Luer lock of the Trachojet. The position of the Trachojet was then confirmed visually using a fibreoptic scope passed down the lumen of the LMA alongside the cannula. The two instruments were then removed from the LMA and the patient reconnected to the fresh gas flow. Nitrous oxide was added and the concentration of volatile agent decreased accordingly and surgery proceeded. Only one insertion of the Trachojet was attempted in each patient. No patient showed signs of inadequate depth of anaesthesia.

Data recorded included patient age and weight, size of LMA used and if insertion of the LMA or

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*Table 1* Number of patients requiring a size 3 or 4 LMA, number of easy and difficult insertions of both the LMA and Trachojet, and the corresponding number of successful tracheal cannulations

| | Tracheal placement | Extra-tracheal placement |
|---|---|---|
| Size 3 LMA ($n$=76) | 22 | 54 |
| Size 4 LMA ($n$=24) | 5 | 19 |
| Easy insertion of LMA ($n$=85) | 25 | 60 |
| Difficult insertion of LMA ($n$=15) | 2 | 13 |
| Easy insertion of Trachojet ($n$=61) | 17 | 44 |
| Difficult insertion of Trachojet ($n$=39) | 10 | 29 |

Trachojet was easy or difficult (more than two attempts). The final position of the Trachojet was recorded as either having entered the trachea or not. Statistical analysis was performed with chi-square tables (StatView 1.04, Apple Macintosh) and a value of $P<0.05$ was considered statistically significant.

We studied 100 patients, with no exclusions. Mean age of the population was 47 (range 22–83) yr and mean weight 68 (47–87) kg. The Trachojet passed into the trachea in only 27 patients. In 12 patients the cannula caught on the lip on the posterior wall of the aperture behind the grill. In the remaining 61 patients it passed into the oesophagus and the piriform fossae in 43 and 18 patients, respectively.

The number of patients with a size 3 or 4 LMA is shown in table 1. There was no significant difference in the success rate of tracheal cannulation in relation to the size of LMA used or if the LMA or Trachojet were inserted with ease or difficulty ($P$=0.07 and $P$=0.1, respectively) (table 1). The aspiration test was 100% accurate in determining tracheal and oesophageal placement of the Trachojet when inserted fully down the stem of the LMA. The test gave a false positive result in the 12 patients in whom the Trachojet impinged on the grille. However, as the cannula could not be inserted fully it was appreciated in each case that the Trachojet had not entered the trachea before confirmation with the fibreoptic scope.

## Comment

Securing a patent airway, supplying oxygen and protecting the lungs from aspirated stomach contents are vital aspects of CPR. Some resuscitation drugs may be administered into the lungs via the trachea and this may be invaluable when i.v. cannulation cannot be obtained. Usually these aims are achieved by tracheal intubation but, occasionally, this may not be possible. Indeed in a multicentre study of 164 patients in which nurses used the LMA as an initial method of airway maintenance and ventilation at cardiac arrest, the trachea could not be intubated in 11 (7%) patients and it was necessary to reinsert the LMA.[3] Clearly, if a vein had not been cannulated in these patients, cardiac drugs could not be administered via the tracheal route. In order for resuscitation drugs to reach the trachea it would be necessary for them to be delivered via a cannula placed within the lumen of the LMA.

Previous investigations have demonstrated variable success in the placement of similar devices into the LMA. Alison and McCrory reported a success rate of 84% in passing a gum elastic bougie blindly down the LMA into the trachea as part of a difficult intubation technique.[4] Successful tracheal placement of an unspecified airway exchange catheter via the LMA has also been reported in a patient who's trachea was difficult to intubate.[5] However, Brimacombe and Berry reported a success rate of only 30% in placing a Cook airway exchange catheter in the trachea of 20 patients when passed blindly down an LMA.[6] The high failure rate was attributable to the catheter being too rigid and having insufficient curvature so that the catheter emerged from the posterior aspect of the aperture thereby favouring oesophageal placement.

The Trachojet is anatomically curved and when it is inserted into the stem of an LMA *in vitro* it emerges on the anterior aspect of the aperture, thereby favouring tracheal placement. However, our success rate *in vivo* was only 27% and was similar to the findings of Brimacombe and Berry.[6] In 12 of our patients the cannula impinged on the posterior lip of the aperture and could not be passed further. *In vitro* it was clear that, if the stem of the LMA was flexed to simulate its passage between the tongue and the posterior pharyngeal wall, then the Trachojet emerged on the posterior aspect of the aperture, so favouring oesophageal placement, despite its curve. All patients had the head extended on the neck when the cannula was inserted to optimize the direction of passage of the Trachojet and coincidentally reducing the flexion of the stem of the LMA. When viewing the final placement of the cannula it was noted when the fibreoptic scope reached the grille of the LMA that the oesophagus was visible in only one of 100 patients and that in this case the cannula had entered the trachea.

We conclude that further modification to the LMA may be necessary before it can be used in conjunction with cannulae such as the Trachojet for administration of drugs during cardiopulmonary resuscitation.

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# Low-dose mivacurium supplementation of prilocaine i.v. regional anaesthesia

J. M. TORRANCE, B. M. F. LEWER AND D. C. GALLETLY

**Summary**

We have compared in two groups of five healthy volunteers, the motor effect of prilocaine i.v. regional anaesthesia of the forearm with and without addition of mivacurium 0.6 mg. Although addition of mivacurium might, theoretically, provide the benefit of increased neuromuscular block with rapid plasma cholinesterase degradation in the isolated limb, we observed prolonged forearm weakness in the mivacurium group using tests of grip strength (median recovery to 90% of control, 80 min (range 60 min to >8 h) *vs* control median recovery to 90% of 16 (8–24) min) and bead transfer (median recovery to 90% of control 36 (24–48) min *vs* control median recovery to 90% of 12 (8–16) min). This weakness was considerably in excess of that predicted by rapid systemic degradation of mivacurium. The mivacurium group experienced symptoms of local anaesthetic toxicity which did not occur in the control group and which could not be replicated by administration of mivacurium alone. (*Br. J. Anaesth.* 1997; **78**: 222–223).

**Key words**
Neuromuscular block, mivacurium. Anaesthetic techniques, regional. Anaethetics local, prilocaine.

Forearm fractures are commonly reduced as outpatient procedures using i.v. regional anaesthesia (IVRA). These fractures often cause muscle spasm which increases bone impaction and the traction that is required for fracture reduction; IVRA with local anaesthetic alone provides poor neuromuscular block. Paralysing the arm by adding a small dose of neuromuscular blocking agent to the local anaesthetic has been shown to facilitate fracture reduction, decrease the pain experienced by the patient both during and after the procedure, and may obviate the need for hospital admission and general anaesthesia in some muscular young patients.[1–3]

Many different neuromuscular blocking agents have been used in small doses with few reported side effects other than transient diplopia and difficulty with accommodation. These include tubocurarine 1 mg, gallamine 10 mg, atracurium 2–5 mg, suxamethonium 4 mg and decamethonium 0.2 mg.[2 3] Ideally, to limit the systemic effects of the neuromuscular blocking agent on deflation of the cuff, the blocker should have a shorter duration of action than the duration of cuff inflation. Atracurium undergoes Hoffmann degradation under mild alkaline conditions and should decay spontaneously in the isolated limb. However, most studies have demonstrated that atracurium produces prolonged paralysis when used to supplement IVRA, which may in part be caused by decreased Hoffman degradation related to the acidic environment of the ischaemic limb.[1 2 4]

Mivacurium is hydrolysed by plasma cholinesterase and may therefore be degraded in the isolated limb provided there is sufficient plasma cholinesterase activity after exsanguination of the limb which must inevitably be incomplete. In this study mivacurium was added to IVRA with 0.5% prilocaine and its effect on the development of motor block and on the return of motor function was investigated. Earlier studies with suxamethonium, which is also degraded by plasma cholinesterase, have yielded conflicting results.[3] If degraded in the isolated arm, mivacurium would confer the benefits of ease of reduction and decreased pain with a low risk of systemic effects.

## Methods and results

We studied 10 healthy, fasted and consenting volunteers in a double-blind, controlled study that was approved by the Wellington Ethics Committee. I.v. cannulae (22-gauge) were sited in the dorsum of both hands and the IVRA was performed on the non-dominant arm. The limb was elevated for 1 min and an upper arm tourniquet inflated to 300 mm Hg. Volunteers were allocated randomly to one of two groups of five subjects (age and weights were not significantly different, one female in each group) to receive either 0.5% prilocaine 40 ml (control) or 0.5% prilocaine 40 ml with mivacurium 0.6 mg (mivacurium group). The tourniquet remained inflated for 20 min after injection of local anaesthetic.

Immediately before drug injection, baseline

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neuromuscular strength and co-ordination were assessed and these were repeated every 4 min until the test variables had returned to baseline or 2 h had elapsed. Crude grip strength was measured by recording the maximum pressure generated by asking the subject to maximally compress a rubber bulb connected to a pressure gauge. The number of beads transferred from one container to another in 15 s with a pair of forceps was used as a test of fine motor skills. Complete neuromuscular block was defined as complete loss of all voluntary movement in the fingers, hand and arm below the cuff.

Complete forearm muscle paralysis occurred in none of the controls and in only two subjects in the mivacurium group and then only after 18 min of limb ischaemia. Muscle strength decreased rapidly in both groups while bead transferral decreased more rapidly in the mivacurium group.

Time to recovery of grip strength to baseline, after deflation of the tourniquet, was significantly more rapid in the control group than in the mivacurium supplemented group (Mann–Whitney *U* test, $P<0.004$). Median time from tourniquet deflation to recovery to 90% of baseline grip strength in the control group was 16 (range 8–24) min. Recovery in the mivacurium group was prolonged (median 80 min (range 60 min to >8 h)). Three of the volunteers who had received mivacurium had not achieved baseline strength within the study duration of 2 h and in one subject grip strength had not returned to baseline 8 h later. Time to baseline recovery of fine motor skills for the bead transfer test was significantly slower in the mivacurium group (Mann–Whitney *U* test $P<0.004$). Median time for return to 90% of baseline of bead transfer was 12 (8–16) min in the control group and 36 (24–48) min in the mivacurium group. Although not specifically tested, there appeared to be no qualitative difference in return of sensation between the two groups.

All volunteers who had received mivacurium in the prilocaine ischaemic arm block spontaneously volunteered symptoms of light headedness, dizziness, perioral paraesthesia, tinnitus, diplopia, blurred vision, altered hearing or slurred speech. These symptoms began 1–2 min after deflation of the tourniquet and lasted for 5–15 min. No adverse effects were volunteered by subjects in the control group. When mivacurium 0.6 mg was injected i.v. into one of the volunteers who had experienced these adverse effects, none of these symptoms of presumed local anaesthetic toxicity was experienced, apart from diplopia which lasted for 10 min.

Two of the five volunteers who received mivacurium developed urticarial weals on the arm several minutes after cuff deflation. One had experienced some pruritus while the cuff was inflated. Neither had a history of atopy.

## Comment

Our results demonstrated that supplementation of prilocaine IVRA with mivacurium resulted in prolonged muscle weakness on cuff deflation, as has been reported with other non-depolarizing neuromuscular blocking agents. This slow recovery suggests that mivacurium is not broken down in the ischaemic limb and that recovery of neuromuscular function is not dependent on plasma concentration, which would be expected to decrease rapidly with washout and dilution on reperfusion of the limb to concentrations too small to affect recovery of the block.[5] Recovery from a drug effect is dependent on plasma concentration only if the plasma concentration decreases slowly; however, if the plasma concentration decreases rapidly, then recovery of neuromuscular function is related to the transfer of mivacurium from the biophase to the plasma. Feldman, Wu and England[5] postulated the presence of binding sites that form a reservoir of drug close to the receptor. Recovery from non-depolarizing neuromuscular blocking agents would therefore reflect not only binding to the acetylcholine receptor but also the kinetics of binding to the reservoir binding sites.

All volunteers who received the combination of mivacurium and prilocaine displayed symptoms of local anaesthetic toxicity that were absent in the control volunteers. Apart from diplopia, none of the symptoms was reproduced when mivacurium 0.6 mg was given i.v. to a volunteer who had demonstrated these side effects. Despite the small numbers, these symptoms were a consistent finding and occurred with a far greater incidence than the 1–2% incidence of minor adverse reactions reported in the literature for IVRA.[6] This interaction has not been reported in previous studies and may warrant specific investigation.

Development of urticarial weals would suggest an increase in vascular permeability. The fact that normal intravascular hydrostatic pressure only occurs on deflation of the tourniquet would explain the delayed development of the urticarial weals.

In summary, mivacurium increases the degree of paralysis of the forearm when added to IVRA, although as with other blocking agents, the neuromuscular blocking effect has a duration well in excess of that of tourniquet inflation.

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CASE REPORT

# Anaphylaxis associated with, but not caused by, extradural bupivacaine

S. M. RAE, M. K. MILNE AND J. A. W. WILDSMITH

## Summary

Identifying anaphylaxis and determining its cause during anaesthesia can be very difficult. We describe a patient who suffered a life-threatening reaction which was diagnosed originally as being caused by bupivacaine. Subsequent investigation and enquiry showed that this was not so and suggested latex as the likely true cause. (*Br. J. Anaesth.* 1997; **78**: 224–226)

**Key words**
Anaesthesia, obstetric. Anaesthetic techniques, extradural. Anaesthetics local, bupivacaine. Complications, anaphylaxis.

Allergy to amide local anaesthetics is rare, but has been reported.[1] More common is the patient who is labelled as being allergic to these drugs when this is not the case. Given the significance of the diagnosis, and the problems it produces for dental treatment in particular, it is essential to confirm the true situation in such patients. The following case report illustrates these issues.

## Case report

A 33-yr-old woman with a history of immune complex disease, but no evidence of vasculitis, presented for elective Caesarean section. She was not receiving any medication and had no drug allergies. She had previously undergone an emergency Caesarean section under uneventful extradural block with bupivacaine and was happy to receive the same anaesthetic again.

Approximately 1 h before the procedure she received 30 ml of sodium citrate 0.3 mol litre$^{-1}$ and ranitidine 300 mg, but no sedative medication. On arrival in the anaesthetic room, her systolic arterial pressure was 120 mm Hg and heart rate 90 beat min$^{-1}$. An extradural catheter was inserted at the fourth lumbar interspace and a total of 18 ml of 0.5% bupivacaine was injected in increments. At 25 min a bilateral block to T2 had developed, but surgery was delayed by an emergency elsewhere. During the interval she was kept in the left lateral position, arterial pressure decreasing only to 105 mm Hg and heart rate remaining unchanged. At 40 min, preparations for surgery began with urethral catheterization in the wedged, supine position. Immediately after catheterization her arterial pressure decreased to 70 mm Hg systolic, but responded initially to increments of i.v. ephedrine. However, she then became nauseated, vomited and developed persistent hypotension. Surgery was started and she required 2200 ml of i.v. crystalloid and increments of ephedrine and metaraminol to maintain systolic pressure at 100 mm Hg before delivery. The baby was born in good condition (Apgar score 9 at 1 and 5 min) 13 min after skin incision.

After delivery the patient became acutely breathless and clinically cyanosed, and arterial pressure could not be recorded, although peripheral pulses were palpable. She lost consciousness and her trachea was intubated after administration of suxamethonium 100 mg. I.v. frusemide and increments of adrenaline were administered for suspected pulmonary oedema and left ventricular failure. She remained hypotensive (systolic arterial pressure 65 mm Hg) and tachycardic (150 beat min$^{-1}$) and at this point developed a generalized erythematous rash. During the procedure she lost an estimated 500 ml of blood and received Syntocinon 10 u. At the end of the operation she was transferred to the intensive therapy unit where artificial ventilation was continued. Arterial pressure responded to 2800 ml of colloid and 1 u. of red cell concentrate. She was noted to have marked peripheral oedema. Coagulation screens remained normal throughout and there was no evidence of amniotic fluid in the maternal blood samples. Her trachea was extubated 5 h after admission to the unit and the following day she was transferred to the postnatal ward where her subsequent recovery was uneventful.

An anaphylactic drug reaction was considered as the explanation for this event and advice was sought from the National Adverse Anaesthetic Reactions Advisory Service, Sheffield. Blood samples for radioallergosorbent tests were obtained and that for suxamethonium was negative. No test was available for bupivacaine, but a diagnosis of a specific reaction to bupivacaine was thought likely and the patient was advised to avoid future exposure to bupivacaine. It

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was considered that intradermal testing would not be helpful.

Subsequent to this event, dental work was carried out uneventfully (as it had been previously) using 3% prilocaine with octopressin, but then local infiltration for further treatment was performed using 2% lignocaine with adrenaline 1 in 80 000. After this the patient developed a severe headache which was probably an adrenaline reaction, but she was concerned that she was experiencing allergy to yet another local anaesthetic drug and was referred, some 7 yr after the original event, to the anaesthetic department for further investigation.

A review of her medical and dental notes was undertaken and revealed that she was known to the dentists to be allergic to latex, but this information was not in the medical notes. Given this fact, and the temporal relationship of the original collapse to insertion of the bladder catheter, it was felt that the latter was the more likely cause of the acute event. Investigations revealed that latex catheters were in routine use in the labour unit at the time of the reaction. Challenge testing with local anaesthetic drugs was agreed with the patient to eliminate them as the cause of her problem and so that further dental treatment could proceed. With appropriate safeguards a series of intradermal injections was performed. At 10-min intervals 0.1-ml increments of normal saline, 0.01% lignocaine, 0.1% lignocaine, 0.05% bupivacaine, 0.5% bupivacaine and 0.5% prilocaine with methyl paraben were injected. The test drugs produced no more erythema than the saline control, and therefore 1% lignocaine 1 ml was injected s.c. before, finally, 0.5% bupivacaine 1 ml was given i.v. There was no reaction.

## Discussion

An adverse reaction to a local anaesthetic agent may result from the systemic effects of the drug or the nerve block it produces, an allergic reaction to some component of the solution, a vasovagal reaction to the situation, or may be temporally, but not causally, related to administration of local anaesthetic. This patient was stable for 40 min before developing hypotension and subsequent loss of consciousness. Systemic toxicity, inadvertent spinal anaesthesia and allergy to some component of the local anaesthetic solution are unlikely as all would be expected to present within minutes of drug administration. The patient did not become bradycardic and this makes a vasovagal event unlikely also. Extensive sympathetic block could produce some of the features seen, but would not explain the generalized erythematous rash or the later oedema, and arterial pressure was stable until preparation for surgery. Turning her to the supine wedged position for catheterization might have compromised arterial pressure, but would not have produced the other features. Hypotension, respiratory difficulty and rash are compatible with an immunological reaction and we propose that this was in response to either the antiseptic (Hibitane) or the urethral catheter, with ranitidine therapy and extensive sympathetic block compounding the situation. Syntocinon might cause such a reaction, but none was administered until well after it had commenced. Reports of allergy to skin antiseptics are beginning to appear[2] and latex allergy is well documented.[3 4] Given that she is now known to be allergic to latex this seems the most likely cause of the reaction. More recently she was accidentally exposed to latex and developed skin oedema and swelling at the point of contact. A further deterioration in her condition occurred after delivery and Syntocinon could have contributed to this.

In this patient, anaphylaxis was diagnosed with the onset of the rash. The diagnosis is easy when cardiovascular collapse is immediately associated with bronchospasm and cutaneous signs, but the latter only appear in 65% of cases.[5] The differential diagnosis of these symptoms in the absence of cutaneous manifestations is difficult and includes not only anaphylaxis, but also drug overdose, haemorrhage, air emboli, bronchial intubation, aspiration, etc. Fortunately, and despite difficulties in diagnosis, treatment is often the same: adequate oxygenation, with sympathomimetic drugs and i.v. fluids. If anaphylaxis is thought possible, potential antigens must be sought and exposure terminated. This patient eventually responded to treatment, but recovery took several hours, probably because the urinary catheter was not suspected as the cause and was left *in situ*. There are no investigations that can be performed during a reaction that aid diagnosis or acute management, but estimation of serum tryptase concentration approximately 1 h after onset is helpful in the subsequent investigation.[6 7] This test was not available at the time of our patient's reaction. After the patient's recovery a detailed history of the event, and examination of all past notes, should be undertaken in an attempt to ascertain the cause of the reaction. If our patient's latex allergy had been documented in her medical notes she would not have been exposed to latex and one of the drugs she received would not have been blamed for the reaction.

If the history suggests anaphylaxis rather than anaesthetic misadventure, or serum tryptase concentration is increased, skin prick testing, as recommended by the recently published Association of Anaesthetists' Guidelines (*Anaphylactic Reactions Associated with Anaesthesia*) may be undertaken to try and establish the cause of the reaction. These guidelines recommend that all reagents administered around the time of the reaction should be used in testing, in addition to a range of agents that may be used in the future. Our patient was challenge tested with local anaesthetic agents because of her concern about continued use. There was no real benefit for her in being tested for latex or Syntocinon, which she had refused in any case. There is ample clinical evidence from her dental attendances that she reacts to latex with skin swelling and oedema, and testing would have exposed her to a small, but real risk of life-threatening anaphylaxis. She intends having no more children and so will not be exposed again to Syntocinon.

Intravascular injection is not recommended in routine testing because a severe response is likely if the true antigen is injected. In this patient's case intravascular injection with bupivacaine was performed because she expressed a wish to be certain that she was not allergic to this drug. It was felt that this was a safe procedure because there had been no reaction to intradermal bupivacaine and the history clearly suggested latex as the true cause of the original problem, although Syntocinon cannot be totally excluded from a contributory role. The testing did prove definitively that the patient was not allergic to local anaesthetic drugs, and the case illustrates clearly the need to consider all aetiological possibilities when anaphylaxis occurs during anaesthesia.

## Acknowledgement

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# CORRESPONDENCE

## Flow cytometry

Sir,—With regard to the article by Heine and colleagues,[1] we believe that several points require clarification.

The authors claim that the technique using 123-dihydrorhodamine is more specific than the more well known chemiluminescence technique for measuring neutrophil respiratory burst. Such claims remain unsubstantiated. Readers may infer from the article that the chemiluminescence method is of less value than the authors' technique. The chemiluminescence technique is not non-specific. It is based on the production of light by activated cells in the presence of enhancers such as luminol or lucigenin. The production of light is dependent on the presence of superoxide anion and hypochlorous acid (produced from superoxide). Singlet oxygen does not produce light in this system.[2]

The only apparent benefit of the dihydrorhodamine technique is its flow cytometry base, allowing the study of a single cell population within a mixed cell environment. However, in the study by Heine and colleagues[1] such benefit is negated by separation of individual cell populations. The cell separation technique as presented is unclear. The layering of whole blood onto Ficoll-Hypaque density medium would result in a mononuclear cell layer with all granulocytes sedimenting with erythrocytes. However, the light scatter diagrams show mixed cell populations comprising monocytes, lymphocytes and granulocytes. It is difficult to see how the data relate to the methodology given or the need for cell separation in the first place.

The propofol carrier, 10% Intralipid, inhibited respiratory burst of granulocytes in an identical manner to that of propofol.[1] However, any effect of Intralipid on either light scatter or light quenching in the flow cytometry system is not discussed. In addition, cited literature has been misquoted. Intralipid was not shown to suppress T cell-mediated immunity as stated.[3] Other studies have confirmed this finding.[4] The effects of lipid emulsions on cell function are dependent on cell type and whether or not the study involves isolated cells *in vitro* or cells after *in vivo* lipid exposure.[3–6] In addition, the antioxidant effects of propofol have not been discussed.

Finally, the use of isotonic saline to dissolve thiopentone and methohexitone preparations inevitably resulted in hypertonic solutions. This may be inappropriate because hypertonic solutions induce a stress response, affect cell function and may also affect respiratory burst activity.[7 8] Pre-exposure of cells to anaesthetic agents before stimulation with PMA[1] implies that the results may represent the effect of the drugs on protein kinase C rather than on NADPH oxidase directly. This factor is not discussed. Protein kinase C is also affected by hypertonic solutions.[9]

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Sir,—We thank Drs Galley and Webster for their interest, however, we are not in accordance with the majority of their comments concerning our article.[1]

They stated that the only apparent benefit of the dihydrorhodamine technique appears to be its flow cytometry base. With regard to our study design, the most important difference between the applied technique compared with chemiluminescence is that the dihydrorodamine technique involves actual measurement of the activity of the respiratory burst oxidase. This enzyme is responsible for intracellular superoxide anion production.[2] In our study respiratory burst activity of only viable neutrophils was analysed in a whole blood system. As the number of analysed events in flow cytometry is practically unlimited, data with low variation coefficients are produced and sensitivity can be increased. Sedimentation at 1 g and 22 °C was used as a reduction of erythrocytes in the whole blood samples, as shown in the light scatter diagrams.[1] Thus no centrifugation or erythrocyte lysis was required and preactivation or impairment of neutrophil function was avoided. This does not imply that chemiluminescence itself is a less valuable method and we did not state so in our article.

Furthermore, Drs Galley and Webster claim that the effect of Intralipid on either light scatter or light quenching in the flow cytometry system had not been discussed in our article. We described in detail the effects of 10-fold anaesthetic doses of propofol and Intralipid on side scatter signals (SSC) in the results and also in figure 5. Figure 5 was given as an example of the decrease in SSC signals of neutrophils which were incubated with the 10-fold anaesthetic doses of propofol. We discussed further if the changes in the cell membrane structure induced by lipid solutions may provide an explanation for the observed decrease in the SSC signals.

We apologize for citing the article of Monson and colleagues who reported stimulation of T cells by lipid solutions under impairment of T cell-mediated immunity.[3]

Suppression of intracellular enzyme respiratory burst oxidase by i.v. anaesthetics is in the first instance an immune compromising effect. It would have been very speculative to discuss a possible antioxidant effect of propofol only on the basis of our *in vitro* experiments.

PMA is a well known and accepted stimulus for respiratory burst which acts directly via protein kinase C.[2]

Finally, control experiments (data not shown in article) with the studied anaesthetics and no PMA stimulation excluded preactivation of neutrophils. Thus the hypertonity of the solutions did not affect the results of the particular system of the study.

The effect of three different lipid solutions (concentration 600 $\mu g\ ml^{-1}$) on respiratory burst under different stimuli was investigated in a consecutive study not yet published. We studied long-chain triglycerides (Intralipid 10, Pharmacia), LCT/MCT preparation (Lipofundin MCT 10%, Braun) and omega-3 fatty acid (Omegavenos 10%, Fresenius). Suppression of respiratory burst by all three lipid solutions under PMA stimulation (% mean inhibition: Intralipid, 87.9 (SD 8.5), Lipofundin, 78.8 (17.0), Omegavenos, 84.3 (10.7)) was found to be similar to previously described results.[1] Under stimulation with *E. coli*, respiratory burst was suppressed by Intralipid (8.0 (9.3)) and Omegavenos (9.6 (11.1)) and increased by Lipofundin (−42.7 (21.4)). Therefore, suppression of respiratory burst by lipid solutions seems to depend both on the stimulus and nature of the lipid solution.

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## ASA classification and perioperative variables as predictors of postoperative outcome

Sir,—I read with interest the article of Wolters and colleagues[1] and I have a comment on their statistical analysis.

They stated "the Student's *t* test was used to quantify the difference in the means of independent perioperative variables between ASA classifications". This test can be used correctly between no more than two groups and it is not used to quantify the difference but just to verify if a difference between means probably exists.[2]

The authors did not report the SD of values of operation duration (min), intraoperative blood loss, intensive care stay (days) or postoperative stay (days) in relation to ASA, but considering preoperative status in relation to hours of postoperative ventilation they report the following mean (SD) values: arterial hypertension yes 7.3 (37.3), no 6.5 (29.8); previous myocardial infarction yes 13.7 (52.2), no 6.4 (34.3); severe bronchopulmonary disease yes 10.6 (45.5), no 5.7 (32); smoker yes 6.3 (30.8), no 6.9 (37).

Parametric tests such as the Student's *t* test or analysis of variance can be used correctly only if the distribution of the variable is symmetrical; when a variable has only positive values and the SD is greater than the mean, the variable must be considered non-symmetrically distributed,[2] and therefore parametric statistics cannot be used to describe or verify a hypothesis on such data.

If the authors had used logistic regression for specific postoperative complications they would have avoided these problems and they would have obtained more useful results than to define risk factors for indefinite "postoperative complications".

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Sir,—We appreciate the comments of Magi on our article. Indeed we used the Student's *t* test to explore observed differences between the means of selected variables for each of two defined subgroups in order to quantify the probability that this differences exists by chance sampling only, as stated in the first sentence on p. 219 "...in relation to ASA (table 6) we found an increase in duration of operation between ASA I and ASA II–IV combined ($P<0.05$) and between ASA II and III ($P<0.05$)...".

In the next step we used explorative *P* values as hints to select some variables as possible predictors for postoperative outcome by modelling the probability of a postoperative complication using a logistic regression model.

We agree with Magi in pointing out some well known general rules of thumb for the correct use of the *t* test, which should be followed, especially when comparing means for small samples.

Additionally, it should be remarked that the methodological properties of the two-sample *t* test may be poor for small samples, even if the data are distributed normally, if sample sizes and variances differ greatly. On the other hand, for sample sizes that are large enough (as for the data in our article) well known implications from central limit theory assure that the *t* test performs well (as for the data in our article) distributions. This "robustness" of the *t* test implies that for "large" samples and without the assumption of normality, the nominal *P* value is approximately the same as the true significance level whenever the null hypothesis holds.

We apologize for giving SD values only for operation duration, postoperative stay and some other variables for the complete sample (c.f. table 2) but not in relation to ASA subgroups. This omission was designed to prevent table 6 from becoming too large.

We again emphasize that the central aim of the study was an attempt to quantify the importance of ASA classification and well known clinical risk factors in the evaluation of complicated surgical outcome by multivariate analysis of clinical data

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## ASA classification and perioperative variables: graded anaesthesia score?

Sir,—As Wolters and colleagues[1] pointed out in discussion, a major drawback of the ASA system is assessment of a patient's "correct" ASA classification by different anaesthetists. This has been shown clearly in previous studies[2 3] in which, after consideration of audit, we have concluded that the preoperative status cannot satisfactorily be described by it alone. The situation in obstetric anaesthesia is no better.[4] Wolters and colleagues overcame this problem by using two experienced anaesthetists to classify each case, which is far removed from routine UK practice.

We believe that an improved scoring system needs to incorporate both physical status (chronic health evaluation) and operative risk. It must be both reproducible and simple to use. The present situation could be greatly improved by combining a minimally modified ASA physical status classification with an indication of relative "anaesthesia risk", thereby producing a composite graded anaesthesia score (GAS).

Anaesthesia risk is multifactorial, but attempts to incorporate this into a physical status/chronic health score create difficulties and inconsistencies, particularly in respect of patients suffering

*Table 1* Graded anaesthesia score (GAS). Morbidity/mortality related to anaesthesia provision for patients with chronic stable intercurrent medical conditions is *not* an additional risk. Additional risks include: (a) acute exacerbations/disturbances in chronic disease states; (b) condition for which surgery is required; (c) proposed surgical plan and its urgency; (d) trauma; (e) physiological disturbances; and (f) anaesthesia influencing conditions (for example 2=dental work, pseudocholinesterase abnormalities, URTI etc; 2.5=aspiration risk, normal pregnancy, moderate obesity, chronic airway management problem, age <1 or >80 yr, anaesthesia related allergies etc; 3=malignant hyperthermia susceptibility, moderate physiological disturbances following trauma, sepsis or head injury, pre-eclampsia, etc; 4=acute airway obstruction, eclampsia, severe physiological disturbances following trauma, sepsis or head injury, morbid obesity, etc)

| Chronic health/physical status | Additional anaesthesia risk |
|---|---|
| 1. A normal healthy patient | 1. No additional risk |
| 2. A patient with mild systemic disease | 2. Minor |
| 2.5. A patient with moderate systemic disease | 2.5. Moderate |
| 3. A patient with severe systemic disease that limits activity but is not incapacitating | 3. Major |
| 4. A patient with an incapacitating systemic disease that is a constant threat to life | 4. Life threatening |
| 5. A moribund patient who is not expected to survive for 24 h with or without an operation | |

trauma or severe acute physiological disturbances such as those induced by sepsis.

Remove concern regarding additional anaesthesia risk by grading it separately, concentrate on intercurrent chronic health concerns and the ASA physical status classification system becomes reliable and reproducible requiring but one small modification in respect of a class between II (mild systemic disease) and III (severe systemic disease) to represent the moderate systemic disease which so frequently presents. ASA V is already effectively a composite score.

The GAS is shown in table 1. It can be seen that all but ASA V patients move from a single to a double digit score with significantly improved "risk assessment". This is of value to quality assurance, in assigning the appropriate grade of anaesthetist and to medical audit, producing the consistency which would thereby allow meaningful comparison between units. Thus the normally healthy patient with a dental abscess producing acute airway obstruction is scored GAS 1.4 and the cases listed by Owens, Flets and Spitznagel[2] and Haynes and Lawler[3] can also be easily and conveniently graded.

Having confirmed the simplicity and ease of use of GAS in a pilot evaluation, we believe that the advantages of the score should now be the subject of a large study on a regional or national basis.

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1. Wolters U, Wolf T, Stützer H, Schröder T. ASA classification and perioperative variables as predictors of postoperative outcome. *British Journal of Anaesthesia* 1996; 77: 217–222.
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Sir,—We are well aware of the problem of consistency in the use of the ASA physical status classification by different anaesthetists. Therefore, in this study we attempted to eliminate this inaccuracy. In addition, the ASA system is used by all anaesthetists in our clinic.

In order to mimic a "real-life" scenario, Haynes and Lawler[1] did not provide a definition of the ASA grades to respondents. In this case it would have been interesting to know if the respondents were regular users of the system. However, Haynes and Lawley and also Plumer and Rottman[2] did not provide any information on this point.

In our study, ASA classification was used only in its original meaning to describe physical status, not as an estimation of anaesthetic risk. The perioperative variables representing outcome were mainly surgical or general perioperative complications and were not manifestations of specific anaesthetic risk, for example aspiration, airway obstruction or malignant hyperthermia.

Therefore, the aim of our study was different from the proposed graded anaesthesia score (GAS) which is intended to represent anaesthetic risk.

We would be very interested to see if the prognostic value of GAS can be confirmed statistically in a large study.

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1. Haynes SR, Lawler PGP. An assessment on the consistency of ASA physical status classification allocation. *Anaesthesia* 1995; 50: 195–199.
2. Plumer MH, Rottman R. How anesthesiologists practise obstetric anesthesia. *Regional Anesthesia* 1996; 21: 49–60.

## Effect of Sprotte needle orientation on spinal anaesthesia

Sir,—I wish to comment on the study of James and colleagues on the effect of orientation of a Sprotte needle on spinal anaesthesia using 0.5% plain bupivacaine.[1] They demonstrated that when the needle orifice was pointing cephalad, median onset time of sensory block to T4, measured by loss of cold sensation, was significantly faster compared with caudad orientation (5 (interquartile range 3–5) min *vs* 8 (5–9) min, respectively). This is a small but clinically useful difference when rapid onset is required. However, the maximum level of sensory block was similar in all four groups which implies that the distribution of local anaesthetic within the cerebrospinal fluid (CSF) was also similar. This is to be expected as the major determinants affecting distribution of local anaesthetics after subarachnoid administration are the physical characteristics of the local anaesthetic and patient characteristics.[2] The technique of injection is less important although it may play a role

The baricity of 0.5 % plain bupivacaine is slightly hypobaric at body temperature.[3] Plain bupivacaine has been shown to "float" cephalad 80–115 min after injection.[4] If injecting in a cephalad direction delivered a higher dose of local anaesthetic to the trough of the thoracic kyphosis, the drug should then "float" upwards along the cephalad border of the kyphosis to a higher level if the patient is in the supine position. The fact that this did not occur implies that a similar dose of local anaesthetic was distributed towards the trough. Hirabayashi and colleagues have demonstrated that the lowest point of the thoracic hollow is T7–T9, which may account in part for the variable spread seen in clinical practice.[5]

Two reasons may explain the lack of difference in maximum spread of local anaesthetic drug in this study. An injection speed of 5 ml $\text{min}^{-1}$ through a Whitacre needle produced turbulent mixing in an *in vitro* model.[6] Also, changes in body position affect the volume of the extradural venous plexus which can consequently displace CSF.[7] It would be easy to imagine the effect in a confined CSF compartment of these two factors resulting in the drug being thoroughly and similarly mixed whatever the initial direction of the needle orifice.

Other studies investigating the effects of orifice orientation of needles with a lateral eye have produced mixed results regardless of the baricity of the drug used.[8–11] Those studies which demonstrated a higher block with the orifice pointing cephalad did so because patients had no or very little body movement after spinal anaesthesia was performed [8–10] In the study of James and colleagues, patients were placed from the right lateral to the left lateral position, and in another study were changed from the sitting to the lateral position.[1 11]

It is difficult to establish if baricity or bulk displacement of CSF is the major factor responsible for the effects caused by changes in body position. Until a truly "isobaric" local anaesthetic mixture is available (tetracaine crystals which can be dissolved in CSF are not available in the UK) positional effects will always have a prominent role over orifice orientation in determining drug distribution within the CSF. While "non-isobaric" agents are favourable in some circumstances there are arguments against their use.[12]

Finally, the angle of emergence of solutions injected through a modern 25-gauge Whitacre needle into a fluid medium is approximately 35° to the longitudinal axis.[6] The angle is approximately 30° with a 24-gauge Sprotte because of the larger orifice (although the size of orifice has recently been reduced) The clinical consequences of this small difference are unknown but are unlikely to be important as a similar distribution pattern of injectate was produced by both of these needles in an *in vitro* model.

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Sir,—We agree that many factors influence the maximum sensory block height achieved after injection of local anaesthetic into the subarachnoid space. Serpell stated that the physical characteristics of the local anaesthetic agent and patient characteristics are more important in determining maximum sensory block than the technique of injection. Our study showed that the technique of injection affected not maximum sensory block but *speed of onset* of block.

The patients we described were pregnant women. The main finding of our study was that the technique of injection for subarachnoid anaesthesia affected the onset time of a sensory block suitable for Caesarean section in women at term. We orientated the side eye of the Sprotte needle cephalad, caudad, right and left lateral, and demonstrated that a cephalad injection produced a significantly faster onset of block. This is a clinically important difference when rapid onset of sensory block is required for Caesarean section.

Maximum block heights achieved were similar regardless of needle orientation so while the speed of onset of block was affected by injection technique, final distribution of local anaesthetic in the CSF is influenced by the many other factors the author mentioned. Posture is particularly important in the pregnant woman at term.[1] We induced subarachnoid anaesthesia in the right lateral position and then turned the women supine with a 20° left lateral tilt and this would enhance the spread of local anaesthetic in the CSF.

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1. Russell IF The effect of posture during induction of subarachnoid analgesia for Caesarean section. *British Journal of Anaesthesia* 1987; **59**: 342–346

## Cardiac arrest after Caesarean section

Sir,—Having read the case report of Scull and Carli,[1] we wish to bring to your readers' attention a similar incident which occurred in our institution recently A 31-yr-old woman was scheduled to undergo an elective lower segment Caesarean section (LSCS) under subarachnoid anaesthesia at 38 weeks' gestation because of a breech presentation. The woman was 163 cm tall and weighed 75 kg.

The patient was premedicated with ranitidine 150 mg and metoclopramide 10 mg, 2 h before operation and 30 ml of sodium citrate 0.3 mol litre$^{-1}$ before induction. After giving 500 ml of colloid i.v., subarachnoid anaesthesia was performed with the patient in the sitting position using 0 5% hyperbaric bupivacaine 2.4 ml injected via a 24-gauge Sprotte needle at L2–3.

The patient lay down on the operating table which was immediately tilted approximately 25° to the left. Arterial pressure before subarachnoid injection was recorded at 129 mm Hg systolic (Dinamap), and after 5 and 10 min was recorded at 114 and 105 mm Hg systolic, respectively. After the second of these readings, ephedrine 6 mg was given i.v. At 10 min block height was T3 bilaterally.

At 15 min as surgery commenced, the patient suddenly complained of severe nausea and became increasingly agitated, talking incoherently and flailing her arms. Arterial pressure had just been recorded at 96 mm Hg systolic, and another dose of ephedrine 6 mg was given i.v. After this the patient continued to flail her arms about, but had stopped talking.

After a few seconds of arm-waving, she collapsed and very rapidly became cyanosed. Her pupils were not dilated at this or at any later time. The ECG monitor showed a bradycardia of 15–20 beat min$^{-1}$, but arterial pressure was not measured at this time. Oxygen saturation was noted to be 70%.

Cricoid pressure was applied and manual ventilation with 100% oxygen started via a face mask. The following drugs were given in rapid sequence: atropine 0.6 mg, ephedrine 18 mg, thiopentone 100 mg and suxamethonium 100 mg, and the patient's trachea was intubated with a 8.0-cuffed oral tracheal tube The pulse oximeter showed a rapid increase in saturation from 70% to 100% before intubation, and this was maintained above 97% after intubation. Anaesthesia was maintained with 1% isoflurane and 50% nitrous oxide in oxygen. Arterial pressure was recorded at 170 mm Hg systolic just after intubation, with a heart rate of 110 beat min$^{-1}$.

The operation continued uneventfully and 1 h 15 min after the subarachnoid injection the patient's trachea was safely and uneventfully extubated. The patient could feel a dull ache in the area of the incision, although the block was not formally tested.

The patient was subsequently interviewed at length. She remembers being unable to breathe or communicate this problem but being still able to move her arms, which she did in order to attract attention. She remembers the mask being applied to her face and air being blown through her nose.

While these are unusual features, this case probably also represents a reduction in venous return (because of aorto-caval compression) leading to bradycardia, hypotension and loss of consciousness. Subarachnoid block has increasingly become the anaesthetic of choice for Caesarean section, particularly in those patients in whom intubation is predicted to be difficult. What this and other cases of respiratory difficulty after subarachnoid anaesthesia[2–6] should remind us is that there is occasionally a requirement for tracheal intubation and any anaesthetic plan should take this into account. Care should also be taken to avoid all causes of a reduced venous return.

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## Dose–response curve for anaesthetics based on the Monod–Wyman–Changeux model

Sir,—Iwai and his colleagues[1] have matched the Monod–Wyman–Changeux (MWC) ligand-receptor model to sigmoid dose–response curves for anaesthetics. The model represents the way in which the proportion of receptor sites occupied increases with increasing concentration of ligand (anaesthetic) Therefore, it seems logical to match the model to the response of a single cell to an anaesthetic when that response can be measured, as in the case of a $Cl^-$ current. Indeed, it is fascinating to see that, when the authors matched the model to the response of induced $Cl^-$ currents in single cells to halothane, they obtained plausible values for the variables of the MWC model.

If depth of anaesthesia can be measured in a single, whole organism, it would also be reasonable to extend the approach to matching the response of that organism to an anaesthetic. Indeed, mathematically, the model can be matched to any sigmoid curve, so it is not surprising that when the authors matched a dose–response curve for isoflurane in humans,[2] they obtained a close match to the reported $EC_{50}$ (MAC) and $EC_{95}$ values.

However, I question the logic of this extension from the response of a single cell or a single organism to the response of a population. The doses are of a comparable nature; the responses are different: in individuals, percentage of maximum response; in a population, percentage of individuals in whom a particular response is present. For example, MAC is the concentration at which 50% of patients fail to respond to a noxious stimulus, classically surgical incision.

The relevant distinction between single organisms and populations is as follows. The variation in the concentration required to produce different $Cl^-$ currents in a single cell, or different depths of anaesthesia in a single patient, arise from the need for different degrees of occupancy of some receptor (or possibly combination of receptors).[3] On the other hand, the variation in concentration required to anaesthetize different patients is presumably as a result of variation in genetic and, perhaps, nutritional and environmental factors.

To take an extreme case, suppose that the dose–response curve for depth of anaesthesia in a single organism has a slope which can be matched with an MWC curve with plausible values for its variables. Suppose then, that 1000 clones of that organism were produced and reared under identical conditions. Those clones would all reach any given depth of anaesthesia (such as lack of response to a noxious stimulus) at the same concentration. Thus at just less than the critical concentration, none of the organisms would respond; at just greater, all would respond. Therefore, the population dose–response curve (for the proportion of organisms responding) would have infinite slope, and yet the dose–response curve (for depth of anaesthesia) for each individual would still have the original slope.

The results of this study are very interesting and will, I hope, stimulate further work in this area. However, I think that the authors are a long way from demonstrating that the variables of reaction kinetics related to depth of anaesthesia can be deduced from population dose–response curves.

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Sir,—Dr Mapleson questioned the logic of our extension of the treatment based on the Monod–Wyman–Changeux (MWC) model from *in vitro* cases to *in vivo* cases in our article.[1] He mentioned that the dose–response of a population is different from that of a cell: if clones were reared under the same conditions, the population dose–response curve would have infinite slope, and yet the dose–response curve for each individual would still have the original slope. Dr Mapleson's argument is correct, provided that some additional integrated effects do not take place in an organism. He also suggested that the variation in the concentration required to anaesthetize different patients is caused by genetic and, perhaps, nutritional and environmental factors. It is plausible. However, we are aiming to understand the mechanism of anaesthesia on the basis of molecular scheme and our article is one of such studies. As mentioned in our article, we assumed that the variation in concentration came from the variation in fractions of active receptor molecules occupied by anaesthetics between individual patients from a molecular viewpoint.

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## Failed intubation drill

Sir,—We read the article by Hawthorne and colleagues[1] with interest.

We agree that there may be a cultural explanation for the disproportionate representation of Afro/Caribbean women presenting for Caesarean section under general anaesthesia. It is well known in the West Indies that West Indian women are reluctant to accept extradural analgesia; indeed, there is no extradural service in our hospital. Further, there may be a higher Caesarean section rate among Afro/Caribbean women because of the increased angle of inclination which predisposes to malposition.[2] On the basis of the above, one may expect to find a higher rate of Caesarean sections under general anaesthesia and by inference more frequent failed intubations.

In the St James' Hospital failed intubation drill it is stated that on deciding that intubation has failed, the patient is turned on her side and placed head down. We disagree with turning the patient on her side and with placing her head down before the return of spontaneous respiration for the following reasons: (a) the key principle in the management of a failed intubation is oxygenation without aspiration.[3] In order to achieve oxygenation, it may be necessary to ventilate the patient's lungs with a bag and mask until the action of suxamethonium terminates; (b) ventilation would be easier if the patient were kept in the supine position with the wedge in place In the head down position, splinting of the diaphragm is aggravated with concomitant reduction of lung compliance thus making lung inflation more difficult; (c) junior anaesthetists are far more experienced at holding a mask and ventilating patients' lungs in the supine than in the left lateral position; and (d) Rosen cautions against turning the patient on her side before the return of spontaneous respiration because this is often impractical and it may be difficult to ventilate the lungs in the lateral position.[4] Afro/Caribbean women at term are quite heavy (average weight in our hospital is 85 kg). It may be difficult to turn her on her side and manage the airway at the same time, and it is quite possible that in the turning process the patient may fall off the table.

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*British Journal of Anaesthesia* 1997; **78:** 232

# BOOK REVIEWS

*Pharmacology in the Practice of Anaesthesia.* L. KAUFMAN AND P. V. TABERNER (editors) Published by Arnold, London. Pp. 689; indexed; illustrated. Price £75.00.

This textbook is the latest entry in a very competitive area of pharmacology textbooks relating to anaesthesia and is edited by an anaesthetist and a pharmacologist The 675 pages of text are divided into 12 sections, containing a total of 39 chapters to which 52 authors have contributed. The authors are principally British; there is one contribution from each of the USA, Canada and Australia.

The 12 sections of the book are divided into general pharmacology, anaesthetic agents, drugs acting on synapses and neuroeffectors, cardiovascular system, respiratory system, central nervous system, management of pain and inflammation, peripheral organ systems (blood, kidneys and GI tract), endocrine system, chemotherapy, sterilization and finally, adverse effects of drugs. Each of these sections consists of usually three or four chapters. Within each chapter there are a reasonable number of figures and tables and each section concludes with, in the majority of cases, a list of five or six texts (often other textbooks) under the heading, recommended reading, although in a few chapters there is an extensive reference list.

I am afraid I found this textbook rather disappointing I had high expectations of it given its editorship but I found it both difficult to read and lacking in information in some areas. One of the approaches to reviewing a textbook is to use it as a reference manual over a period of time. In doing this, I found that while in general the anaesthetic drugs are dealt with reasonably well (although often in short note form) there are other areas where the information is rather diffuse and there are confusing cross-references in the text. Examples of these are: in the i.v. anaesthetic agents, each agent is dealt with in less than one page and the pharmacological information is comprehensive but not exhaustive. Examples of the gaps that I encountered were in the relationship to adrenoreceptors where after a virtually unlabelled diagram in the first chapter, the text said it would be explained in further chapters. Despite searching I could not find a comprehensive description of G-protein involvement and the method of transmission across the cell membrane. In the chapters on opioids, there is confusion between the authors of two consecutive chapters as to whether sigma receptors should be included, with the first stating they are not opioid receptors as they are insensitive to naloxone and some 12 pages later the second author notes that they are opioid receptors which are similar to kappa in being weakly sensitive to naloxone. There are some good sections within this book and indeed overall this reflects the difficulty of multi-authorship textbooks.

There are now seven or eight textbooks dealing with anaesthetic pharmacology and I am not sure how this textbook will fare in this very competitive market.

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*Reflex Sympathetic Dystrophy: A Re-appraisal.* W. JANG AND M. STANTON-HICKS (editors). Published by IASP, Seattle. Pp. 249; indexed; illustrated. Price $55.00.

In 1993, a conference in Florida, USA, addressed the controversy surrounding reflex sympathetic dystrophy (RSD) and a consensus was reached concerning a re-definition of this complex syndrome. The topics included in *Reflex Sympathetic Dystrophy: a Re-appraisal* were chosen during discussion after this conference but the editors are keen to emphasize that the book is not simply a description of the proceedings of that conference. They are to be congratulated in persuading such an eminent and international panel of authors to contribute to the volume.

The first chapter describes very clearly and comprehensively the mechanisms and hypotheses surrounding RSD. It is an excellent opening chapter and provides the background for the rest of the book. Despite the consensus to adopt the term complex regional pain syndrome (CRPS), both terms are used throughout the book. For simplicity, the reviewer will use CRPS only.

The second chapter describes the clinical characteristics of CRPS (both I and II) based on data collected from two clinics in Germany. A comprehensive analysis includes factors such as changes in skin temperature under various conditions and results of diagnostic tests. Although this is a very localized audit, it is likely that the results and conclusions will be of great interest to all practitioners worldwide. Similar data from a USA clinic follow and the authors have arrived at a recommendation on the diagnosis of CRPS based on a clinical and laboratory approach.

The final chapter in this section deals with CRPS in children, the differential diagnosis of the syndrome and the development of a diagnostic algorithm. These early chapters give the reader a very wide appreciation of the syndrome of CRPS and the controversies surrounding its aetiology and diagnosis.

The book now considers the influence of animal models on our understanding of CRPS. Three animal models of neuropathic pain (chronic constriction injury, partial nerve transection and spinal nerve transection) are reviewed. The authors have selected data relevant to CRPS and have not reviewed extensively other less relevant data. I thought this chapter was particularly good; the literature was reviewed critically and important conclusions emerged.

The various mechanisms mediating pain in neuralgia are considered next. This difficult area is discussed well, aided by many very helpful figures and diagrams. A logical next step is to consider sensory testing in patients with CRPS; many methods of testing are considered and all are possible at the bedside or in the clinic.

Chapters on the use of placebo and psychological issues in CRPS follow. Again, these are excellent contributions and it is concluded that the "RSD personality" is not substantiated. Finally, there is a small and precise review on the use of regional anaesthesia for diagnosis of CRPS.

I found this book a delight to read; there cannot be a better treatment in a relatively small publication of this complex area. I am sure it is essential reading, not only for those who are training in pain management, but for those who are already established. It certainly represents very good value for money.

*D. J. Rowbotham*

*British Journal of Anaesthesia* 1997; **78:** 233

## ERRATA

*British Journal of Anaesthesia* 1996; 77: 686P.

In the sixth sentence of the second paragraph, the equation is printed as:
"Gastrointestinal transit was assessed using the "geometric centre" (the centre of gravity) (=(CiSi)/Ci, where Ci=count in segment Si).[1] "
This should read as follows:
"Gastrointestinal transit was assessed using the "geometric centre" (the centre of gravity) ($=\Sigma(CiSi)/\Sigma Ci$, where Ci=count in segment Si).[1]"

*British Journal of Anaesthesia* 1996; 77: 526–529.

The name of one of the authors was misprinted. Dr Masakazu Hayashi*da* was erroneously spelt as Masakazu Hayashi*ta*.

We apologize to the authors for this confusion.

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*"I would have everie man write what he knowes and no more."*—MONTAIGNE

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## EDITORIAL I

### Extracorporeal membrane oxygenation, a favourable outcome?

Extracorporeal membrane oxygenation (ECMO) uses a pump oxygenator to provide prolonged respiratory or cardiac support in the intensive care unit. Since the first successful use of ECMO was reported in 1972[1] there have been conflicting opinions on the use of ECMO to salvage moribund patients. The American National Institute of Health (NIH) study showed no survival advantage compared with conventional treatment[2] and a virtual cessation of ECMO in adults followed the publication of this study. However, a mortality rate of more than 60% for ARDS patients[3] forced intensivists to continue to search for successful therapies; partial liquid ventilation,[4] inhaled nitric oxide,[5] prone ventilation[6] and pressure control inverse ratio ventilation (PCIRV)[7] have all been advocated. All of these modalities may result in improved blood-gas tensions, and some in improved survival.[7] Unfortunately, while such improvements may be statistically significant we are still faced with the clinical problem of a mortality rate of 82%[8] to 55%[7] from severe ARDS. It is likely that the small response in terms of survival lies in the fundamental problem that any treatment which relies on the injured lung to maintain gas exchange will become increasingly ineffective as lung disease becomes more severe, mortality increasing from 33% with moderate lung injury to more than 82% with severe injury,[8] because of continued barotrauma,[9] volutrauma[10] and oxygen toxicity,[11] all combining to produce ventilator lung injury.[12] Eventually a point is reached when the airway pressure, minute volume and $F_{I_{O_2}}$ necessary to maintain life exceed the lungs capacity to resist the continual and repeated insults of ventilation, and thus the patient perishes. We return therefore inexorably to the concept that some form of extrapulmonary gas exchange coupled with gentle ventilation, "lung rest", which causes no further damage to the "baby lung"[13] is the most rational treatment for refractory severe respiratory failure, provided any significant morbidity associated with the treatment itself can be minimized or eliminated. The intra-vena caval oxygenator (IVOX)[14] needs further development in terms of gas transfer capability and clinical ease of operation before it becomes a viable option, as in its current form only modest reductions in ventilator settings, which is the goal of extrapulmonary gas exchange, are possible. Thus ECMO remains the only current technique which can support gas exchange outside the lung, and allow the lung to be rested and recover. Numerous case series, summarized by Lewandowski and colleagues,[15] have shown that ECMO, including extracorporeal carbon dioxide removal (ECCO2R) can result in similar or reduced mortality (51%) compared with conventional treatment (56%)[15] but is usually applied only to patients with more severe disease. Unfortunately the intensive care community in general remains unconvinced as to the purported benefits of ECMO, as there are difficulties in comparing different historical series of patients treated in different hospitals, at different times, with different severities of illness and different treatment techniques. A recent attempt to solve this conundrum was the randomized study of ECCO2R *vs* PCIRV[16] conducted by Morris and colleagues. No significant difference was apparent between the 58% mortality in the PCIRV group and the 69% mortality in the ECCO2R group. This study was interpreted by the authors and the sceptics to confirm the findings of the earlier NIH study, that ECMO is ineffective, but the methodological and technical considerations discussed by Rossaint and colleagues in this issue of *British Journal of Anaesthesia*[17] make this conclusion unguarded. However, it is safe to conclude from the data of Morris and colleagues that low-flow ECCO2R, even when provided by an inexperienced team, and when complicated by haemorrhage and technical problems, is as good as the very best PCIRV.

Full flow (i.e. enough to provide oxygenation and carbon dioxide removal) veno-venous ECMO has been shown to be effective in supporting gas exchange, allowing a reduction in ventilation and $F_{I_{O_2}}$.[15 17–19] While there are reasonable concerns on the use of historical controls when comparing different treatments, common sense indicates that if these results have been duplicated by numerous different ECMO providers around the world, and if consultants continue to refer their moribund patients for ECMO, the most likely explanation is that ECMO is effective.

This conclusion is supported by comparing our own series of adult respiratory patients with the patients described by Morris and colleagues.[16] For the first 50 patients referred to us for treatment, mean $P_{a_{O_2}}/F_{I_{O_2}}$ ratio was 8.7 (SD 4.9) kPa, not significantly different from the control group of Morris and colleagues (*t* test, $P=0.741$), the Murray score[20] was 3.4 (0.5) and hospital mortality 34%, a significant improvement over the best published series of patients undergoing conventional ventilation (58% mortality)[16] (chi-square 11.71, $P=0.0006$).

Assuming that one accepts the benefits of ECMO with lung rest, the problem of transporting the critically ill, hypoxic patient to a hospital providing ECMO still remains. Our own experience is that while this may often be possible, patients who are extremely hypoxic, especially those who are dependent on inhaled nitric oxide, can be very unstable during transfer, and usually need to be "crashed on" to ECMO on arrival at our hospital. The answer to this problem is initiation of extracorporeal support at the referring hospital and transfer of the patient back to the ECMO centre on ECMO in a calm, unhurried manner. Rossaint and colleagues[16] have reported their experience with eight extremely hypoxic patients transported on veno-venous ECMO; there were six long-term survivors. A 25% mortality for patients with an $Pa_{\mathrm{O}_2}/FI_{\mathrm{O}_2}$ <6.7 kPa and a mean Murray score of 3.59 is impressive even if transport were not involved.

This experience confirms the observation of other ECMO transport teams, that if the patient's gas exchange can be supported extracorporeally, patients can be stabilized and transported many thousands of miles in safety.[21,22] Other authors have elected to use mainly veno–arterial perfusion during transport to provide more haemodynamic control, and then convert to veno-venous support when the patient has been stabilized back at the ECMO centre. Another curious fact to emerge from series of patients transported on ECMO is that the outcome in this group of patients too ill to be moved by conventional means is often better than patients transported to the ECMO centre using positive pressure ventilation. The University of Michigan group reported a mortality rate of 14% for adult ECMO transport patients[21] compared with 43% for other adult ECMO patients.[23] This may indicate that patients should be referred for ECMO earlier, before severe hypoxia is established, or alternatively that mobile ECMO should be used more widely.

Mobile ECMO is now available in the UK, as the Heartlink ECMO centre at Glenfield Hospital, Leicester, now has transport facilities. The mobile ECMO system has been used once thus far to transport a 2-yr-old boy with Kawasaki syndrome to a transplant centre; the patient remained stable during transport despite absent underlying myocardial function but, unfortunately, heart transplantation 1 week later was not successful.

Intensivists who are sceptical about the potential benefits of ECMO should audit (and publish) the mortality of their patients with hypoxic acute respiratory failure. If they can show consistently better mortality than 34% for a mean $Pa_{\mathrm{O}_2}/FI_{\mathrm{O}_2}$ of 8.7 kPa and Murray score of 3.4 then they are justified in continuing to treat their patients conventionally; if however they cannot, it is in their patients' best interests to consider the benefits of ECMO when conventional treatment is failing, and before terminal ventilator lung injury has occurred (7 days).

Unfortunately, many intensivists remain sceptical. Indeed the editorial accompanying the publication of the UK Collaborative Neonatal ECMO study,[24] stated that ECMO was an "unfavourable outcome".[25] If one believes this then considering the evidence one must therefore consider death and disability to be preferable to ECMO. We do not believe this to be the case.

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*British Journal of Anaesthesia* 1997; **78**: 238–240

## EDITORIAL II

# Are there new solutions to old problems with weaning?

Delayed weaning from mechanical ventilation is a problem in every intensive care unit. Not only is this associated with an increased mortality and risk of pneumonia,[1] pulmonary emboli and psychological disturbances,[2 3] but it also has implications for the cost of care and the use of scarce resources.

The question of how to hasten weaning raises several inter-related issues that have a major bearing on our approach to the patient undergoing ventilation. The first is the question of what is meant by the term "weaning". It usually implies two separate but closely related aspects of care, termination of mechanical ventilation and removal of any artificial airway. This may lead to confusion because the definition of mechanical ventilation is becoming more blurred with the increasing variety of modern techniques of support. Continuous positive airway pressure (CPAP), for example, is not strictly a form of ventilation but should a patient with CPAP and an orotracheal tube be considered to be weaned? If the tube is removed and CPAP is provided via a face mask, should the patient now be considered to be weaned although he or she is receiving the same support physiologically? Similarly, is the patient who uses a nasal positive pressure ventilator each night in the home after discharge from an ICU weaned or not? A more satisfactory approach would be to discontinue the term "weaning" and address its two components separately—can independent ventilation and tracheal extubation be achieved?

Mechanical ventilation is required for as long as the load on the respiratory pump exceeds its capacity. The load can be reduced by lowering metabolic rate by treating any infection, and relieving the patient's fear and anxiety. The resistive work of breathing can be reduced by treating reversible airflow obstruction and aspirating secretions in the tracheobronchial tree, and the elastic work can be minimized by treating pulmonary oedema or pneumonia, and avoiding hyper-inflation. Conversely, respiratory drive may be improved by reducing sedation, avoiding sleep deprivation or metabolic alkalosis, and by normalizing arterial $P\text{CO}_2$. Respiratory muscle function can be optimized by attention to the position of the patient, especially if the diaphragm is weak, relieving malnutrition, and correcting hypoxaemia, hypercapnia, acidosis, hypercalcaemia, hypophosphataemia and hypomagnesaemia.

But is this load:capacity concept useful in practice? It has led to the use of several predictors for successful "weaning" such as tidal volume $>5$ ml kg$^{-1}$, FEV$_1$ $>10$ ml kg$^{-1}$, vital capacity $>10$–15 ml kg$^{-1}$, maximum inspiratory pressure $>20$–30 cm $H_2O$, minute ventilation $<10$ litre min$^{-1}$ and a maximum voluntary ventilation of twice the resting minute ventilation.[4 5] Recently more complex measures, including ventilatory frequency to tidal volume ratio and an index combining thoracic compliance, respiratory frequency, $Pa_{O_2}$ to $PA_{O_2}$ ratio and maximal inspiratory pressures have been developed[6] but they, in common with simpler indices, have been found to be of limited value in predicting the success of weaning.[7–9]

There are several reasons why these predictors fail. First, most of the measurements require a maximal effort which is hard to ensure in ill patients in an ICU. Second, there are technical difficulties which have led to poor repeatability of measurements[10] and even if the values are accurate the question remains as to whether or not all important factors relevant to weaning are being measured. None of the methods takes into account the psychological state of the patient or the far reaching autonomic and humoral responses which occur particularly during the first 24 h after tracheal extubation and which alter, for instance, fluid and electrolyte balance, deadspace: tidal volume ratio, cardiac output and regional lung perfusion.[11]

The airway may need to be retained, irrespective of whether or not ventilatory support can be discontinued in order to bypass upper airway obstruction or, more commonly, because of doubt about the patient's ability to cough and swallow. This is a problem, particularly in chronic neuromuscular disorders but also results from both translaryngeal intubation, which may cause vocal cord oedema and ulcers,[12] and tracheostomy. A tracheostomy impairs the elevation of the larynx with its associated opening of the crico-pharyngeal sphincter[13] and also increases the threshold for the reflex for laryngeal closure in response to supraglottic stimulation.[14 15] Co-ordination between the respiratory and swallowing related functions of the larynx is impaired and the risk of aspiration increases.

The immediately apparent problem is how to assess the safety of tracheal extubation while the airway remains in place. The gag reflex, swallowing ability and strength of "coughing" give some information. If there is no preceding upper airway obstruction or known difficulty in swallowing or coughing, and particularly if the period of intubation is short, it is reasonable to extubate the trachea when mechanical ventilation is no longer needed and to observe the patient's upper airway function. The risks are, however, greater if intubation has been prolonged and failure to recognize bulbar problems is a frequent cause of re-intubation.

In the presence of bulbar dysfunction the conventional approach is to maintain the tracheal or tracheostomy tube cuff inflated in order to protect the airway. It is, however, only partially effective in achieving this[16] and tends to perpetuate laryngeal and pharyngeal dysfunction. The opposite strategy of cuff deflation should be considered. Although there is little direct evidence, this probably improves the co-ordination of the laryngeal and pharyngeal muscles through reinstating the respiratory function of the larynx and enabling speech to occur. The air passing through the upper airway probably initiates other currently ill defined reflex actions which improve upper airway co-ordination. The risk of aspiration can be minimized in the early stages by only partially and intermittently deflating the cuff. However, cuff deflation is probably the single most underrated and important step in improving upper airway function in the patient whose lungs are ventilated and it should have a central place in the preparatory phase of weaning.

What can be done to swing the balance between the load and capacity of the respiratory pump in favour of the latter? Does the method of ventilation affect the patient's progress or does it have a purely supportive rather than a therapeutic role? Mechanical ventilation certainly does have a variety of cardiorespiratory effects on, for instance, ventilation:perfusion matching, lung volumes and the work of breathing, but these are largely transitory. They may keep or put the patient in a position from which weaning may take place but they do not alter the balance between the load and capacity of the respiratory pump after tracheal extubation or cessation of ventilatory support. It does have two effects which may, however, hasten the moment of weaning. The ventilatory response to hypercapnia increases if arterial $P\text{CO}_2$ is normalized, and respiratory muscle function can also be modified. Respiratory muscle fatigue is avoided normally by adaptation of the central respiratory controlling mechanisms but it is probably wise to try to avoid the respiratory muscles performing near-fatiguing work during mechanical ventilation. Minimizing respiratory muscle work is thought to be helpful in the early stages of an acute illness and when the patient is systemically unwell but after this the strategy should be changed to progressively increase the work of breathing according to the patient's capacity. The aim is to increase respiratory muscle strength and endurance, reverse any disuse atrophy and improve the co-ordination of the different muscle groups in order to aid the weaning process.

It is, therefore, important to select a method of ventilation that both effectively normalizes blood-gas tensions and enables the respiratory muscles to be rested or conditioned as appropriate. A range of partial support techniques such as assist control, SIMV, with or without pressure support, and pressure support ventilation are in widespread use.[17] The work of breathing can be graduated with each of these techniques but the type of work carried out by the patient is different in each case. There are remarkably little data comparing these methods but pressure support ventilation appears to be associated with a shorter period of intubation[18] and minimizes the risks of diaphragmatic fatigue.[19] Addition of pressure support to SIMV has little influence on weaning.[20] T-piece weaning is also used widely, although there are conflicting data as to whether or not this is more effective than pressure support ventilation or CPAP.[21–23]

There are now a wide variety of positive pressure face and nasal masks and mouth pieces[24] and negative pressure techniques using a tank, jacket or cuirass ventilator which are well established.[25] These non-invasive interfaces are being used increasingly to assist weaning but what do they add to conventional tracheal and tracheostomy tubes? A tracheostomy reduces the deadspace and, in common with non-invasive techniques, enables sedation to be withdrawn; if the cuff can be deflated, speech, swallowing and laryngeal co-ordination improve to a variable degree. The non-invasive methods, nevertheless, have two important advantages: they do not require an artificial airway, which impairs coughing, swallowing and speech, and they can also be used intermittently which makes them suitable for patients who benefit from gradually increasing periods of independent ventilation.

Non-invasive techniques should be considered if progress with the conventional interfaces slows or stops.[26 27] They can be introduced gradually while the tracheostomy is in place, although the positive pressure methods require the cuff to be deflated. They are, however, usually unsuitable if the patient is unconscious, unco-operative, requires continuous ventilation for more than 2 or 3 days, or has a poor cough with profuse secretions. They do not protect the airway and a risk of aspiration is generally considered to be a contraindication to their use. This potential difficulty can, nevertheless, be overcome. The first step is to reduce the risk of aspiration by giving the patient nothing by mouth, reducing the volume of saliva (by administration of propantheline or a tricyclic antidepressant, for example) and by feeding through a gastrostomy. The cuff on the artificial airway can then be deflated, often only partially or intermittently at first, and if aspiration does not occur ventilation using a nasal or face mask can be initiated. When this is established the tracheal or tracheostomy tube can be removed and ventilation continued non-invasively. This may be required for a few days or, particularly in chronic neuromuscular disorders, it may be needed in the long term, but usually only at night.

This approach brings together the parallel tracks of ventilatory support and upper airway management. Their integration is often the key to delayed weaning but this may still be impossible unless a broad approach to rehabilitation is applied.[28] Attention should be paid to nutritional support and mobilization, but especially to the patient's psychological needs. The ability to speak when the cuff is deflated and encouragement that an independent life outside hospital is possible are important factors in improving the patient's morale. A normal sleep–wake cycle should be established and sleep deprivation, which is unavoidable in intensive care units because of the almost continuous sensory stimulation,[29] relieved.

Where does this leave the traditional concept of weaning as cessation of respiratory support or extubation. It is clear that these two events are only points in the continuum of care. They are preceded by the preparation phase in which both the physical and psychological aspects of care are attended to and are followed by the rehabilitation phase and in some patients long term, usually nocturnal, non-invasive ventilatory support at home. It is important to distinguish in the preparation stage between purely supportive care and treatments which hasten the time of weaning. Ventilatory support and tracheal extubation, the two separate aspects of weaning, should be assessed separately but their treatments should not simply be provided in parallel but should be closely integrated. A central aspect of integrative weaning is deflation of the cuff of the artificial airway. This not only improves upper airway function but makes positive pressure non-invasive ventilation feasible. Progress through these stages requires complex psychological adjustments which can be particularly difficult if the patient is sleep deprived as a result of the general level of activity on the intensive care unit.

This broad view of the problems of delayed weaning can produce results which are superior to conventional methods.[30] Much work remains to be done to assess the relative importance, precise indications for and mechanisms of action of each of the components of these new approaches. The expertise and facilities that are needed range from those of an intensive care unit to those of both a home ventilation and a rehabilitation unit. The full range of resources are therefore currently concentrated in only a few specialist centres, but may prove to be required more widely in the future.

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CLINICAL INVESTIGATIONS

# Extracorporeal membrane oxygenation for transport of hypoxaemic patients with severe ARDS

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**Summary**

Conventional inter-hospital transfer of patients with severe acute respiratory distress syndrome (ARDS) in need of extracorporeal membrane oxygenation (ECMO) may be risky and in severe hypoxaemic patients may be associated with cerebral hypoxia and death. Therefore, we began a phase 1 study to evaluate the feasibility, complications and outcome of inter-hospital transport of these patients using veno-venous ECMO. Eight patients with severe ARDS and a $Pa_{O_2}/FI_{O_2}$ <6.7 kPa at a PEEP ⩾10 cm $H_2O$ were placed on a mobile ECMO at the referring hospital. The 495 (SD 123) km inter-hospital transport via a special ground ambulance took 341 (151) min. After transfer, blood-gas tensions were improved in spite of less optimal ventilator settings, compared with data before the start of ECMO. No significant complications occurred. Six patients survived and were discharged from hospital; two patients died because of multiple organ failure. We conclude that initiation of ECMO in hypoxaemic patients before inter-hospital transfer is feasible and enables safe transport to an ECMO centre. (*Br. J. Anaesth.* 1997; **78**: 241–246).

**Key words**

Lung, acute respiratory distress syndrome. Ventilation, mechanical. Hypoxaemia. Monitoring, extracorporeal circulation. Complications, mortality. Intensive care.

The acute respiratory distress syndrome (ARDS) is a rapid and severe alteration in lung structure and function characterized by hypoxaemia, reduced respiratory compliance, pulmonary hypertension and diffuse interstitial infiltrates.[1 2] Since its first description by Ashbaugh and colleagues in 1967, the mortality rate of this syndrome remains greater than 50%, despite extensive clinical and laboratory research efforts.[3–5] Among other unknown factors, this high mortality may be influenced by the disease itself, in addition to iatrogenic factors such as ventilator settings with high airway pressures, large tidal volume and high inspiratory oxygen concentrations ($FI_{O_2}$).[6 7] Therefore, today we aim to reduce peak airway pressure, tidal volume and use lower inspired oxygen concentrations. Conventionally, it is now customary to use pressure- or volume-limited ventilation, or both, with positive end-expiratory pressure (PEEP), body positioning, including prone position, differential lung ventilation, avoidance of fluid overload and acceptance of increased partial pressure of carbon dioxide.

Should these therapeutic measures fail to improve pulmonary gas exchange, extracorporeal lung support has been advocated in the treatment in patients with severe, but potentially reversible, acute respiratory failure.[8 9] As this technique requires special equipment and knowledge, centres for advanced treatment of ARDS have arisen. However, conventional inter-hospital transfer of patients in need of extracorporeal membrane oxygenation (ECMO) can be risky and in severely hypoxaemic patients ($Pa_{O_2}/FI_{O_2}$ <6.7 kPa) may be associated with cerebral hypoxia and death. Therefore, we began a phase 1 study to evaluate the feasibility, complications and outcome of inter-hospital transport using ECMO in this group of patients.

## Patients and methods

This investigation was performed at the Virchow-Klinikum of the Humboldt-Universität with the approval of the institutional Ethics Committee. Informed consent was obtained from each patient's family.

Patients were included in the study if they suffered from severe ARDS, that is a Murray score ⩾2.5[10] and fulfilled the modified fast entry criteria of the US National ECMO study[11] ($Pa_{O_2}/FI_{O_2}$ <6.67 kPa at a PEEP ⩾10 cm $H_2O$ for >2 h) despite various trials to optimize pulmonary gas exchange. Patients were excluded from the study if they had contraindications to ECMO which include extremely poor prognosis because of the underlying disease (malignancy, unresolvable surgical problems), immunosuppression, assured irreversible damage of the central nervous system, severe chronic pulmonary disease,

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*This article is accompanied by Editorial I* primary cardiogenic pulmonary oedema and advanced age (>60 yr). Additional organ failures, such as cardiac, hepatic, renal, CNS, gastrointestinal and haematological failure were assessed using grade II definitions of the score of Goris and colleagues.[12]

From June 1993 to October 1995, nine patients fulfilling the above criteria were referred to our hospital for extreme respiratory failure unresponsive to conventional treatment. The severity, duration and assumed consequences of hypoxia, and other organ failures were assessed by telephone. As one of the nine patients died within 2 h after the first phone call, there were eight patients (table 1) to be transferred to our intensive care unit (ICU).

### TRANSPORT FACILITIES

The ECMO team went to the referring hospital by ground ($n=2$) or air ($n=6$) transit depending on the distance to the referring hospital. The ECMO team comprised two anaesthetists and one nurse who were experienced with ECMO techniques. A large bus equipped as a mobile ICU was used for inter-hospital transfer of patients from the referring hospital to our hospital. This bus contained a blood-gas, haemoglobin and electrolyte analyser (ABL 505, Radiometer, Copenhagen, Denmark), a monitor system (Siemens Elema, Lund, Sweden), infusion pumps and a bed fitted with a Siemens 300 ventilator (Siemens Elema, Lund, Sweden), an independent power and gas supply, and a portable monitor system (Siemens) with ECG, arterial and pulmonary artery pressures and pulse oximetry (fig. 1).

### EXTRACORPOREAL BYPASS AND CANNULATION TECHNIQUE

After arrival at the referring hospital, the patient's condition was assessed by the physician, whereas the nurse started immediately to prepare the extracorporeal bypass system. In three patients, a pulmonary artery catheter was introduced and central venous and arterial catheters were changed; in all patients, a short trial was undertaken to improve ventilator settings, which included a test with different PEEP levels and I:E ratios. If $Pa_{O_2}/FI_{O_2}$ remained less than 6.7 kPa at a PEEP $\geq 10$ cm $H_2O$, veno-venous ECMO was initiated. Cannulation was not performed in the operating theatre but in the ICU with the patient in bed. For venous access, 21F cannulae (Biomedicus) were used for adults and 17F cannulae (Biomedicus) for children. Blood was drained via one or—in order to achieve higher extracorporeal blood flows—two spring wire reinforced cannulae introduced percutaneously via the femoral vein, with one cannula placed in the inferior cava and, if possible, a second cannula advanced to the iliac bifurcation. Blood was drained passively into a collapsible reservoir. This reservoir was equipped with a Servo switch to stop the pump if the reservoir collapsed. From here, blood was pumped actively by an almost occlusive roller pump (Stöckert, Germany) through a microporous membrane lung (Medronic Maxima, Anaheim, CA, USA) which was ventilated with oxygen 3–6 litre $min^{-1}$. Oxygenated blood was then returned to a cannula, also introduced percutaneously from the right jugular vein (seven patients) or from the right subclavian vein (one patient) and advanced to the superior cava. All parts of the extracorporeal system were coated with heparin. The extracorporeal flow rate was adjusted to 1.8 litre $min^{-1}$ in children and to 3 litre $min^{-1}$ in adults. Blood temperature was regulated extracorporeally by a heat exchanger and maintained at 36 °C. Continuous monitoring of pressure before and after the membrane lung allowed detection of a kink in the tubing, unintended reduced extracorporeal blood flow or disconnection within the extracorporeal bypass circuit. All electrical parts of

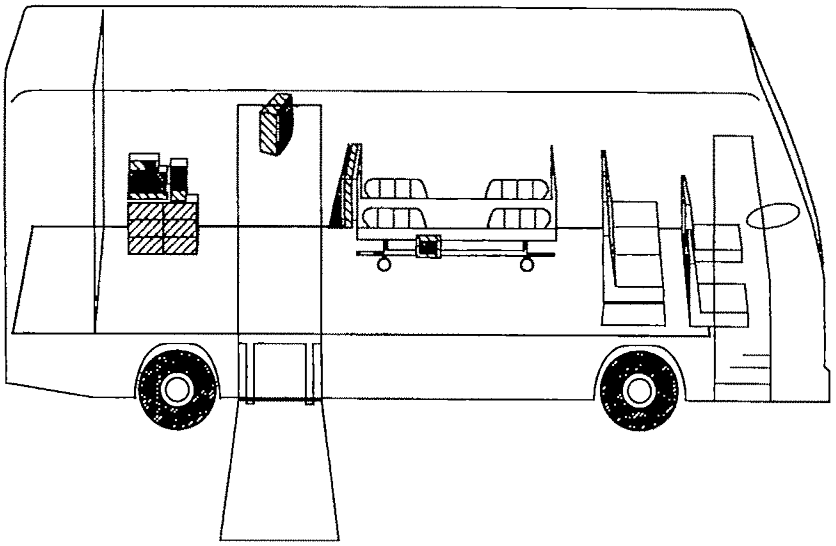

*Figure 1* Intensive care ground ambulance. The bus is equipped with a blood-gas, haemoglobin and electrolyte analyser (in the back of the bus), monitor system, infusion pumps and a bed fitted with a Siemens 300 ventilator, power pack and gas supply, and a portable monitor system with ECG, arterial and pulmonary artery pressure facilities in addition to pulse oximetry. The patient and mobile ECMO are moved into the bus at the same time via a loading ramp.

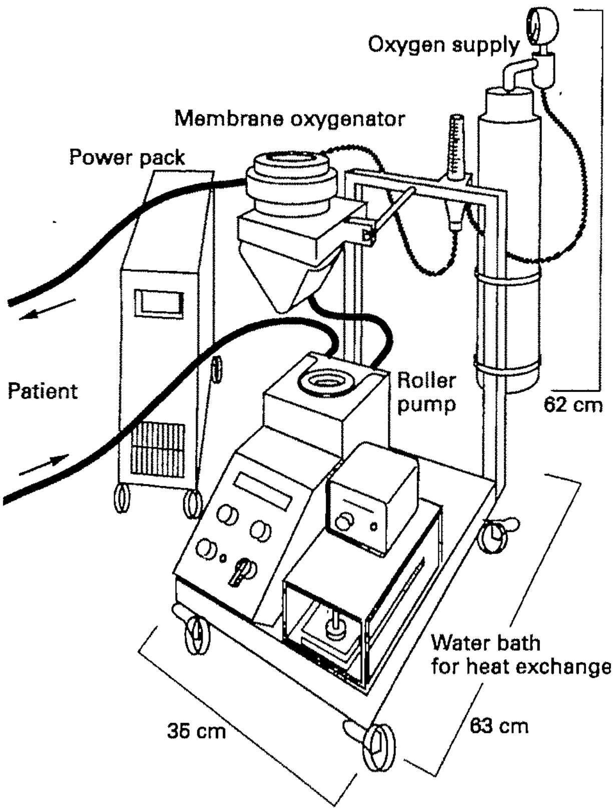

*Figure 2* Mobile ECMO with roller pump, membrane oxygenator, oxygen supply to ventilate the membrane lung, and water bath for heat exchanger. All electrical parts of the mobile ECMO are attached to an independent power pack.

the mobile ECMO unit were attached to a dedicated current powerpack (fig. 2).

The use of surface heparinized equipment reduced the need for heparinization. After an initial bolus injection of heparin 1000–2000 u. immediately before insertion of the cannulae, heparin was infused continuously to maintain the activated clotting time at 120–150 s.

After commencing ECMO, ventilator settings were adjusted for the decreased pulmonary gas exchange needs and to reduce further structural damage produced by high $F\text{I}_{O_2}$, large tidal volumes and/or high peak inspiratory pressures, that is patients' lungs were ventilated with a pressure controlled mode with a ventilatory frequency limited to $\leqslant 10$ bpm, I:E ratio of 1:1, peak inspiratory pressure $<35$ cm $H_2O$ and a PEEP of 9–16 cm $H_2O$. $F\text{I}_{O_2}$ was adjusted to maintain $Pa_{O_2}$ at 8–9.3 kPa. At this time inhaled nitric oxide, which was given to three patients by the referring physicians in order to improve arterial oxygenation,[13] was stopped. Infusions of cardiotonic or vasoactive drugs were continued if necessary, whereas parenteral nutrition was always stopped.

### TRANSPORT OF PATIENTS ON ECMO

After a stabilization period of 1–2 h, the patient was rearranged in the bed of the mobile ICU and connected to its monitor and respirator. The patient was then moved to the mobile ICU in which the patient, together with the ECMO unit, were placed on a loading ramp. The bed and mobile ECMO unit were anchored in the ICU bus. During inter-hospital transfer, ECG, systemic arterial, pulmonary arterial and central venous pressures, $Sp_{O_2}$ and temperature were monitored continuously. Blood-gas analyses were performed hourly.

On arrival at our hospital, a CT scan of the head and lungs was performed followed by measurement of systemic and pulmonary variables, in addition to arterial and mixed-venous blood-gas tensions. Oxygen contents of arterial, mixed venous and capillary blood were calculated and the venous admixture ($\dot{Q}va/\dot{Q}t$) was derived from the Berggren formula.[14] The quantity of extravascular lung water content (Lung Water Computer 9310, Edwards Laboratories, Irvine, CA, USA) was estimated using the double-indicator dilution technique.[15]

### STATISTICAL ANALYSIS

All data are presented as individual values or mean (SD). Differences between values before transport without ECMO and those after inter-hospital transfer with ECMO were analysed using the non-parametric Wilcoxon signed rank test. Changes were considered significant if $P<0.05$.

## Results

Eight patients with a $Pa_{O_2}/F\text{I}_{O_2}$ of 6.7 kPa at PEEP $\geqslant 5$ cm $H_2O$ for $>2$ h because of severe ARDS (Murray score 3.59 (0.23)) induced by multiple trauma or pneumonia were transferred on ECMO to our hospital. Before the start of ECMO, $Pa_{O_2}$ was 5.7 (0.5) kPa and $Pa_{CO_2}$ was 7.9 (1.5) measured at an $F\text{I}_{O_2}$ of 1.0, peak inspiratory pressure of 37.4 (6.1) cm $H_2O$ and PEEP of 12.6 (2) cm $H_2O$ (table 1). The interval between the request to transfer a patient and initiating ECMO was 513 (137) min. The 495 (123) km inter-hospital transport took 341 (151) min (table 2). The only complication related to transport which occurred was a breakage of a stop-cock on the top of the membrane lung during loading onto the bus. As the conus of the stop-cock remained in the membrane lung, the whole membrane lung had to be exchanged. However, the patient survived this event without adverse effects.

After arrival in our ICU, heart rate was 110 (26) beat $min^{-1}$, mean arterial pressure 83 (19) mm Hg, pulmonary artery pressure 29 (8) mm Hg and cardiac index 3.1 (0.3) litre $min^{-1}$ (table 3). Extravascular lung water was high with 33.4 (14.2) ml $kg^{-1}$. Comparing gas exchange variables and ventilator settings before transfer without ECMO with those after transfer with ECMO demonstrated that $Pa_{O_2}$ increased by 3.1 (0.9) kPa ($P=0.012$), and $Pa_{CO_2}$ decreased by 1.9 (1.4) kPa ($P=0.012$), $F\text{I}_{O_2}$ by 0.28 (0.18) ($P=0.028$), peak inspiratory pressure by 8.3 (7.4) cm $H_2O$ ($P=0.036$) and ventilatory frequency by 11.4 (3.4) bpm ($P=0.012$). Total duration of extracorporeal respiratory support was 8 (9) days.

Six patients survived and were discharged from hospital; two patients died as a result of multiple organ failure. In three of the six survivors we observed neurological symptoms after weaning from

*Table 1* Patients characteristics, gas exchange and ventilator settings at the first contact with the referring hospital. The severity of ARDS was determined as described by Murray and colleagues[10]; additional organ failures were determined using the score described by Goris and colleagues.[12] PIP=Peak inspiratory pressure, PEEP=positive end-expiratory pressure, $V_T$=tidal volume, $f$=ventilatory frequency

| Patient No. | Age/Sex (yr) | Diagnosis or risk factor for ARDS | Lung injury score | Other organ failures | Duration of ventilation (days) | $Pa_{O_2}/F_{I_{O_2}}$ (kPa) | $Pa_{CO_2}$ (kPa) | PIP (cm $H_2O$) | PEEP (cm $H_2O$) | $V_T$ (ml) | $f$ (bpm) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 20/M | Multiple trauma | 3.75 | None | 2 | 6.1 | 6.7 | 37 | 15 | 820 | 22 |
| 2 | 35/M | Pneumonia (pneumococci) | 3.75 | Kidney, liver, heart | 6 | 6.0 | 9.0 | 45 | 12 | 250 | 25 |
| 3 | 53/M | Pneumonia (*Klebsiella*) | 3.75 | Heart | 4 | 5.1 | 10.0 | 33 | 15 | 440 | 22 |
| 4 | 8/M | Pneumonia (Epstein–Barr virus and aspergilli) | 3.75 | Heart | 17 | 6.1 | 8.9 | 34 | 13 | 300 | 25 |
| 5 | 51/M | Pneumonia (aspergilli and candida) | 3.75 | Kidney | 7 | 6.3 | 6.8 | 45 | 12 | 580 | 20 |
| 6 | 48/M | Pneumonia (pneumococci) | 3.5 | Kidney, liver, heart | 2 | 5.6 | 6.8 | 42 | 14 | 850 | 18 |
| 7 | 36/F | Pneumonia (unknown origin) | 3.25 | Heart | 2 | 5.3 | 7.1 | 35 | 10 | 800 | 14 |
| 8 | 24/F | Pneumonia (unknown origin) | 3.25 | Kidney, liver | 2 | 5.3 | 6.4 | 28 | 10 | 700 | 20 |

*Table 2* Clinical course of the patients

| Patient No. | Interval request–ECMO (min) | Duration of transport (min) | Duration of ECMO (days) | Duration of ventilation (days) | ECMO flow (litre $min^{-1}$) | Survival |
|---|---|---|---|---|---|---|
| 1 | 435 | 390 | 5 | 10 | 3 | Yes |
| 2 | 365 | 90 | 11 | 11 | 3 | No |
| 3 | 310 | 150 | 3 | 16 | 3 | Yes |
| 4 | 695 | 485 | 28 | 59 | 1.8 | Yes |
| 5 | 475 | 410 | 10 | 36 | 3 | Yes |
| 6 | 595 | 420 | 4 | 4 | 3 | No |
| 7 | 600 | 495 | 4 | 12 | 3 | Yes |
| 8 | 630 | 285 | 2 | 9 | 3 | Yes |

*Table 3* Haemodynamic and gas exchange variables, and ventilator settings after arrival in our ICU. HR=Heart rate, MAP=mean arterial pressure, PAP=mean pulmonary artery pressure, CI=cardiac index, CVP=central venous pressure, PCWP=pulmonary capillary wedge pressure, EVLW=extravascular lung water, $\dot{Q}va/\dot{Q}t$=venous admixture, $F_{I_{O_2}}$=inspiratory oxygen fraction, PIP=peak inspiratory pressure, PEEP=positive end-expiratory pressure, and $f$=ventilatory frequency

| Patient No. | HR (litre $min^{-1}$) | MAP (mm Hg) | PAP (mm Hg) | CI (litre $min^{-1}min^{-2}$) | CVP (mm Hg) | PCWP (mm Hg) | EVLW (ml $kg^{-1}$) | $Pa_{O_2}$ (kPa) | $Pa_{CO_2}$ (kPa) | $\dot{Q}va/\dot{Q}t$ (%) | $F_{I_{O_2}}$ | PIP (cm $H_2O$) | PEEP (cm $H_2O$) | $f$ (bpm) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 102 | 89 | 36 | 3.2 | 10 | 14 | 20 | 9.3 | 5.3 | 54 | 0.6 | 20 | 9 | 7 |
| 2 | 90 | 70 | 35 | 3.5 | 13 | 13 | 38 | 8.1 | 6.4 | 89 | 1.0 | 34 | 12 | 11 |
| 3 | 106 | 98 | 24 | 2.7 | 9 | 11 | 24 | 9.6 | 5.9 | 54 | 0.7 | 29 | 15 | 9 |
| 4 | 159 | 68 | 19 | 2.7 | 6 | 2 | 43 | 8.7 | 7.3 | 83 | 0.7 | 21 | 9 | 10 |
| 5 | 88 | 110 | 28 | 3.1 | 12 | 11 | 28 | 8.4 | 5.7 | 78 | 0.7 | 35 | 16 | 10 |
| 6 | 118 | 63 | 39 | 3.4 | 14 | 13 | 52 | 8.1 | 6.4 | 85 | 1.0 | 36 | 14 | 10 |
| 7 | 82 | 100 | 18 | 3.3 | 6 | 8 | 49 | 9.9 | 4.3 | 72 | 0.5 | 23 | 9 | 8 |
| 8 | 135 | 62 | 34 | 3.1 | 18 | 16 | 13 | 8.5 | 6.4 | 82 | 0.6 | 35 | 14 | 10 |

the ventilator which were thought to be caused by the hypoxia. All three patients recovered nearly completely during the following months.

## Discussion

Despite extensive research and increasing knowledge of the pathophysiology of ARDS, newer studies still show an overall mortality rate of more than 50% without ECMO.[16] In our centre, using a combination of advanced therapy and extracorporeal lung support as a last resort therapy the mortality rate was 27%.[17] However, until recently we refused patients who had a $Pa_{O_2}/F_{I_{O_2}}$ of 5.3 kPa in spite of optimization of ventilator settings, because we believed that these patients would not survive conventional inter-hospital transport. Furthermore, we were anxious to transfer patients with an $Pa_{O_2}/F_{I_{O_2}}$ of 5.5–6.7 kPa as in some of the latter patients transported before the onset of this study, gas exchange deteriorated further during inter-hospital transfer causing periods of arterial oxygen saturation of less than 65%. Boedy, Howell and Kanto reported a 12% mortality rate for transported infants before ECMO could be initiated.[18] For adults with severe ARDS, no data are available. Therefore, we developed a transport ECMO system to facilitate safe inter-hospital transport of patients with a $Pa_{O_2}/F_{I_{O_2}}$ of 6.7 kPa. This study has demonstrated that ECMO for transport of such patients was feasible with good results and no severe complications.

Some clinicians cast doubt on the benefit of extracorporeal lung support on survival in patients with severe ARDS, especially because two randomized, controlled studies failed to demonstrate an increase in survival using ECMO[11] or extracorporeal carbon dioxide removal.[19] The US ECMO study was conducted from 1974–1977 and published in 1979.[11] The results showed no differences in survival rates between patients treated by ECMO and patients undergoing mechanical ventilation alone. Patients treated with extracorporeal bypass and mechanical ventilation, and those treated with mechanical ventilation alone, had a high mortality rate (10% *vs* 8%). However, the ECMO regimen used in the US ECMO study differed markedly from the present method and, in our opinion, is not comparable. The main differences included the use of a high flow veno-arterial bypass potentially inducing insufficient oxygen supply to the lung, non-heparinized systems leading to severe bleeding complications, and mechanical ventilation with high airway pressures and high tidal volumes, possibly further damaging the lung. Moreover, the study was conducted during an influenza epidemic with a high frequency of pneumonia, a cause of ARDS known to be associated with a high mortality rate.[20] Furthermore, the poor results might also have resulted from the study design allowing termination of ECMO if after 5 days of treatment no improvement in lung function could be observed. However, it is well known today that initial improvement in lung function with subsequent survival may occur as late as day 10 to day 20 of treatment.

Similar shortcomings were observed in the second randomized, controlled study conducted from 1987 to 1991 in the pulmonary ICU of the University of Salt Lake City by Morris and colleagues.[19] The purpose of this study was to compare pressure-controlled inverse ratio ventilation (pcCMV-IRV) followed by low frequency positive pressure ventilation with extracorporeal carbon dioxide removal (LFPPV-$ECCO_2R$) with controlled positive pressure ventilation in patients with ARDS. Morris and colleagues found that survival was not significantly different in both groups (33% *vs* 42%), although overall survival rate had improved significantly compared with survival in the US ECMO study. A possible explanation for why Morris and colleagues could not show benefit from LFPPV-$ECCO_2R$ is that they reported 22 bleeding complications in the LFPPV-$ECCO_2R$-treated patients and had to terminate extracorporeal respiratory support in seven of 19 patients because of bleeding problems.[19] In contrast with our routine, Morris and colleagues used extracorporeal bypass with non-heparinized circuits and artificial lungs. The available literature suggests that bleeding remains the most common complication in adult patients with ARDS undergoing extracorporeal lung support, and seems to be related partly to constant heparinization.[8 21–24] Another explanation for the poor survival rates of Morris and colleagues in LFPPV-$ECCO_2R$- treated patients may be the relatively low extracorporeal blood flow rates of 2.38 (SEM 0.01) litre $min^{-1}$.[19] In order to accomplish a significant reduction in iatrogenic lung injury caused by mechanical ventilation, higher oxygen transfer rates would have been necessary, requiring a higher extracorporeal blood flow. In our patients extracorporeal blood flow was approximately 50% of cardiac output which makes limitation of peak inspiratory pressure to $\leq 36$ cm $H_2O$ and $V_T$s to $<10$ ml $kg^{-1}$ in our ECMO patients possible; Morris and colleagues had to apply a mean PIP of 49.5 cm $H_2O$ during the entire LFPPV-$ECCO_2R$ in order to maintain sufficient oxygenation.[19] In our opinion, after commencing pressure- and volume-limited ventilation combined with permissive hypercapnia, the main goal of extracorporeal lung support is to avoid irreversible hypoxic injury. This goal can be achieved using a veno-venous bypass technique with high extracorporeal blood flow and without causing bleeding complications, if heparin-coated systems are used.[9] Obviously, the technique itself cannot heal the lung but allows for sufficient arterial oxygenation in spite of less damaging ventilator settings, as demonstrated in our study. Finally, the extent of practical experience with extracorporeal lung support may also influence the results of clinical studies. Before the start of our study, we had treated more than 35 patients with ECMO, while Morris and colleagues had treated only two patients before they began their randomized clinical study. Although a further prospective, randomized study may be desirable, from our point of view, the positive results in Europe in more than 450 patients with severe ARDS clearly justifies the use of extracorporeal respiratory support as a last resort therapy.[25]

In particular, in the group of patients in this study with an assumed mortality risk of nearly 100%, inter-hospital transport could only be performed without the hazards of hypoxic injury by using ECMO, and six of eight patients survived. Our experience is in accord with that of other groups who consider ECMO to be a feasible alternative to conventional transport for hypoxic neonates or those with an unstable cardiopulmonary sysem,[26 27] or for adults.[28 29] However, to date, transport of patients receiving ECMO is not performed widely because of logistic or technical problems, or both. Using the described technical equipment (mobile ECMO, bed fitted with a ventilator, ICU bus) allowed us to perform all routine intensive care procedures with the exception of x-rays, and therefore this procedure is in accordance with the "Guidelines for the transfer of critically ill patients" provided by the American College of Critical Care Medicine.[30]

Using a ground transport facility for inter-hospital transport of patients led to a mean transfer time of 4.7 h. We are aware that air transport either with fixed-winged aircraft or with a helicopter would have shortened the duration of transport. However, we believe that in patients already receiving ECMO the duration of inter-hospital transfer is less important than adequate space for treatment and full availability of ICU equipment in the ICU bus. The time required for transportation in the ICU bus can be used for further optimization of ventilation and haemodynamic state.

An ECMO transport service is very costly in terms of personnel, vehicles and equipment. Such a service may deprive the ECMO centre of critical care staff for many hours. It would be preferable therefore to transport patients in need of advanced treatment of ARDS[17] at a time when the receiving hospital's ECMO entry criteria are not yet fulfilled. However, four of eight patients transported developed hypoxic respiratory failure and required mechanical ventilation within 2 days of the onset of the disease. Therefore, we believe that there is a need for safe facilities to perform such inter-hospital transport.

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# Propofol anaesthesia and postoperative nausea and vomiting: quantitative systematic review of randomized controlled studies

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## Summary

We have analysed randomized controlled studies which reported the incidence of postoperative nausea and vomiting (PONV) after propofol anaesthesia compared with other anaesthetics (control). Cumulative data of early (0–6 h) and late (0–48 h) PONV were recorded as occurrence or non-occurrence of nausea or vomiting. Combined odds ratio and number-needed-to-treat were calculated for propofol as an induction or maintenance regimen, early or late outcomes, and different emetic events. This was performed for all control event rates and within a range of 20–60% control event rates. We analysed 84 studies involving 6069 patients. The effect of propofol on PONV was dependent mainly on the method of administration, time of measurement and range of control event rates. When all studies were included the number-needed-to-treat to prevent PONV with propofol was more than 9 when used for induction of anaesthesia and at best 6 when used for maintenance. Within the 20–60% control event rate range, best results were achieved with propofol maintenance to prevent early PONV: the number-needed-to-treat to prevent early nausea was 4.7 (95% confidence interval 3.8–6.3), vomiting 4.9 (4–6.1) and any emetic event 4.9 (3.7–7.1). Within the 20–60% control event rate, of five patients treated with propofol for maintenance of anaesthesia, one will not vomit or be nauseated in the immediate postoperative period who would otherwise have vomited or been nauseated. This may be clinically relevant. In all other situations the difference between propofol and control may have reached statistical significance but was of doubtful clinical relevance. Treatment efficacy should be established within a defined range of control event rates for meaningful estimates of efficacy and for comparisons. (*Br. J. Anaesth.* 1997; **78**: 247–255).

**Key words**
Anaesthetics i.v., propofol. Vomiting, nausea. Vomiting, antiemetics. Vomiting, incidence Statistics

Propofol is thought to be antiemetic and therefore useful to decrease the incidence of postoperative nausea and vomiting (PONV).[1–3] However, the mechanism of its effect on PONV is obscure. Interpretations range from propofol being less emetogenic than other anaesthetics[4] to being directly antiemetic.[2] When given in subanaesthetic doses after surgery either as prophylaxis[5 6] or as treatment,[2] results were contradictory.

A biological basis for propofol being an antiemetic is lacking. In animals, propofol did not interact strongly with dopamine D2 receptors[7] and in human volunteers subhypnotic doses of propofol did not prevent vomiting induced by the dopamine agonist apomorphine.[8] These data make it unlikely that propofol has a significant antiemetic effect via dopamine receptors.[9] Results from *in vitro* studies were inconclusive.[10 11] One *in vitro* model suggested that propofol had little or no effect on endogenous 5-$HT_3$ receptors while volatile anaesthetics enhanced 5-$HT_3$ receptor-mediated currents.[10] This may be indirect evidence that propofol has less emetogenic potency than other anaesthetics.[10] In another *in vitro* study propofol was shown to be a potent 5-$HT_3$ receptor blocker.[11] However, in this experiment all of the general anaesthetics examined caused concentration-dependent inhibition of the 5-$HT_3$ channel.[11] Other vague theoretical mechanisms of propofol and antiemesis include direct depressant action on the chemoreceptor trigger zone, vagal nuclei and other centres implicated in nausea and vomiting,[7] or modulation of some subcortical pathways.[2] Although documented anecdotally, propofol-induced improvement of mood and well-being could not be reproduced in a randomized experimental human study.[12]

The evidence is that propofol has only a minimal effect on vomiting in paediatric strabismus surgery, a clinical situation with a particularly high risk of PONV.[13] The aim of this meta-analysis was therefore to test the evidence that propofol, when used for induction or maintenance of anaesthesia, decreases the incidence of PONV compared with other anaesthetic techniques.

## Methods

MEDLINE (Knowledge Server v3.25) was searched (1981 to December 1995) for randomized

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controlled studies which evaluated the effect of propofol compared with other anaesthetics (control) on PONV and reported the outcome in dichotomous form (number of patients with and without an outcome). The search strategy was not restricted to the English language and used combinations of the free text terms emesis, nausea, vomiting, adverse effects (subheading), and propofol, Disoprivan, Diprivan, Disopropofol or ICI35868. Additional reports were identified from reference lists of retrieved reports and from review articles of PONV and propofol. Unpublished studies were not sought. Abstracts were not considered. Reports without randomization or with an inadequate method of randomization (such as patient's date of birth) were excluded from analysis.

Information on patients, anaesthetics, surgery and definition of PONV was obtained from each report. Three different PONV outcomes were extracted in dichotomous form: nausea, vomiting (including retching), and any emetic event (nausea, vomiting or nausea and vomiting). These outcomes were treated separately as "emetic events". Incidences of early (0–6 h) and late (0–48 h) emetic events were extracted. Thus a maximum of three different emetic events could be extracted from each study, both early and late. When several incidences of events were reported at different times the cumulative values nearest to 6 and 48 h after operation were analysed. Emetic events "during recovery" or "after operation" were considered as early data. No weighting was used for different grades of nausea, number of vomiting episodes, time to first vomiting episode, number of patients needing antiemetic rescue medication, delay until discharge or scores of patient satisfaction.

When propofol was used only for induction it was compared with other i.v. or inhalation induction techniques. Propofol as a maintenance anaesthetic was compared with other maintenance regimens. When multiple comparisons were possible between propofol and several other anaesthetics in one study, only one control arm was analysed. The primary choice for control was, for induction, another i.v. agent and for maintenance, an inhalation method. Comparisons where propofol was used as an induction agent in both active and control groups were excluded. Comparisons between a nitrous oxide-free propofol arm (total i.v. anaesthesia) and a nitrous oxide-based control arm were not considered because of the potential effect of nitrous oxide on emesis.[14] However, studies were analysed when nitrous oxide was omitted in both the propofol and control arms.

The plot of L'Abbé, Detsky and O'Rourke[15] of event rates with propofol compared with control event rates was used as a graphical means of exploring the efficacy of propofol and homogeneity of the data set. A scatter predominantly lying between the line of equality and the control axis suggested efficacy with propofol and homogeneity.

Statistical significance and clinical relevance of the efficacy of propofol were evaluated using odds ratio and number-needed-to-treat (NNT)[16] methods. Odds ratio estimates were calculated with 95% confidence intervals (95% CI) using a fixed effects model.[17] Point estimates and 95% CI of the NNT were calculated.[18] The NNT indicated how many patients had to be exposed to propofol in order to prevent one particular emetic event in one of them, who would have had this emetic outcome with a control treatment (that is, with another anaesthetic).

Efficacy was defined as absence of an emetic event. The efficacy of propofol was analysed separately for different modes of administration (induction, maintenance), different times (early, late emetic events) and different emetic events (nausea, retching/vomiting, any emetic event). This was done by combining single propofol or control arms both independent of control event rates (i.e. for all incidences of emetic events with control anaesthetics) and within a range of 20–60% control event rates (i.e. after exclusion of all data from studies with a control event rate less than 20% or greater than 60%). This range of control event rates was a *post hoc* definition.

Absence of a statistically significant improvement of propofol over control was assumed when the lower 95% confidence limit of the odds ratio was <1 or when the NNT point estimate was either negative or its upper 95% confidence limit included no effect (an infinite NNT). For simplification, only NNT with 95% CI are shown. Our arbitrary definition of a clinically relevant effect for prophylaxis of PONV was an NNT ≤5. An NNT of 5 would be the best estimate of efficacy which could be achieved with a control event rate of 20%.

Calculations were performed using Excel v 4.0 on a Power Macintosh 7100/66. Tables with data extracted from the analysed reports, including odds ratios with confidence limits, are available from the world-wide-web (http://www.jr2.ox.ac.uk/Bandolier/painres/propponv.html).

## Results

We considered 122 reports for analysis; 19 were excluded because propofol was used for induction in the control group (11 studies) and/or because nitrous oxide was omitted in the propofol but not in the control group (eight studies) and no other comparisons were possible. Another 19 studies were excluded for various reasons; six were not randomized,[19–24] the randomization method was inadequate in four,[25–28] the technique of maintenance was not mentioned in two,[29 30] three were not adequately controlled (opioid or droperidol only in one group),[31–33] one had eltanolone as the only control arm[34] and data from three studies were published twice.[35–40]

Data from 84 randomized controlled studies involving 6069 patients (3098 treated with propofol) were analysed. A list of these references is given in the appendix. Median group size was 22 (range 10–75) patients. Thirty-one (37%) studies were sponsored by the manufacturer of propofol. Propofol as an induction agent or as a maintenance regimen was compared with other anaesthetic techniques in a large variety of surgical settings in children and adults. Maintenance of anaesthesia with propofol included induction with propofol or an initial bolus of propofol in all studies.

*Table 1* One control arm per emetic outcome and study. Nausea, vomiting (including retching), and any emetic event (nausea, vomiting, or nausea and vomiting) may be reported in one study. *(a) and (c)=number of patients in whom the event was absent; (b) and (d)=the total number of patients in the listed studies. Control event rate=Incidence of emetic outcomes in control group; CI=confidence interval; n/a=not applicable. Early events=0–6 h; late events=0–48 h; ∞=infinity (negative value, indicating absence of a statistically significant difference between propofol and control). Odds ratios with 95% confidence limits are available from the internet (http://www.jr2.ox.ac.uk/Bandolier/painres/propponv.html)

| | All control event rates | | | | 20–60% control event rates | | | |
|---|---|---|---|---|---|---|---|---|
| | Absence of given events | | | | Absence of given events | | | |
| Event | With propofol a/b* | With control c/d* | Number-needed-to-treat (95% CI) to prevent the event with propofol 1/(c/d-a/b) | Reference | With propofol a/b* | With control c/d* | Number-needed-to-treat (95% CI) to prevent the event with propofol 1/(c/d-a/b) | Reference |
| Propofol for induction—early events | | | | | | | | |
| Nausea | 308/354 | 269/353 | 9.3 (6.1–19.4) | [65–77] | 42/63 | 29/62 | 5.0 (2.7–35) | [68], [77] |
| Vomiting | 360/415 | 329/414 | 13.7 (8.1–45.4) | [65–68], [70–81] | 161/197 | 133/197 | 7.0 (4.4–17) | [67], [68], [75–80] |
| Any event | 183/217 | 175/220 | 20.9 (8.3–∞) | [36], [82–87] | 61/77 | 60/83 | 14 (5.0–∞) | [83], [86] |
| Propofol for induction—late events | | | | | | | | |
| Nausea | 81/101 | 79/101 | 50.1 (7.6–∞) | [73], [76], [80], [88] | 48/65 | 45/64 | 28 (5.3–∞) | [73], [80], [88] |
| Vomiting | 107/130 | 99/131 | 14.9 (6–∞) | [73], [76], [88–90] | 62/81 | 54/81 | 10 (4.2–∞) | [73], [76], [88] |
| Any event | no data | no data | n/a | | no data | no data | n/a | |
| Propofol for maintenance—early events | | | | | | | | |
| Nausea | 945/1064 | 790/1035 | 8 (6.4–10.8) | [40], [42–50], [53–56], [68], [73], [75], [77], [91–102] | 418/507 | 310/506 | 4.7 (3.8–6.3) | [40], [42], [47], [50], [53–56], [68], [77], [91], [93–95], [97–100], [102] |
| Vomiting | 1273/1339 | 1098/1304 | 9.2 (7.6–11.7) | [4], [38], [40–56], [68], [73], [75], [77–79], [93–99], [102–108] | 559/608 | 410/575 | 4.9 (4.0–6.1) | [4], [40], [41], [43], [51–56], [68], [75], [77–79], [94], [95], [97], [102], [103], [107], [108] |
| Any event | 399/440 | 311/417 | 6.2 (4.7–9) | [1], [82], [83], [87], [109–119] | 237/263 | 187/269 | 4.9 (3.7–7.1) | [1], [83], [110], [112], [114], [116–119] |
| Propofol for maintenance—late events | | | | | | | | |
| Nausea | 209/228 | 171/230 | 5.8 (4.2–9.4) | [38], [73], [88], [96], [102], [120–123] | 117/133 | 96/134 | 6.1 (3.9–14.5) | [73], [88], [121], [122] |
| Vomiting | 277/346 | 245/349 | 10.1 (6.2–28.8) | [4], [38], [73], [88], [96], [102], [107], [108], [120], [122–125] | 165/217 | 140/219 | 8.3 (4.9–28) | [4], [73], [88], [102], [107], [108], [122] |
| Any event | 64/70 | 57/70 | 10 (4.7–∞) | [126], [127] | 44/50 | 37/50 | 7.1 (3.4–∞) | [126], [127] |

The event rate scatters (fig. 1) suggested improvement with propofol over control mainly for early outcomes when propofol was used for maintenance, and also suggested homogeneity for all data sets. The mean control event rate (incidence of PONV in controls) was 22% (range 0% to almost 70%). For all 84 randomized controlled studies a total of 169 different control event rates (nausea, vomiting or any emetic event) were reported; 77 (46% of all reported events) had an incidence less than 20% and six (4%) an incidence of more than 60%.

### COMBINED ANALYSIS FOR ALL CONTROL EVENT RATES (TABLE 1)

For all control event rates the combined analysis indicated statistically significant results (NNT confidence interval excluding infinity) in favour of propofol for all three PONV outcomes only when propofol was used as a maintenance regimen and only when early events were analysed. Under these conditions, 11–16% of patients (NNT 6.2 for absence of any emetic event, 8 for absence of nausea and 9.2 for absence of vomiting) undergoing propofol anaesthesia will not have an emetic event in the early postoperative period, who would have vomited or been nauseated with another anaesthetic.

When early and late outcomes after propofol as an induction agent or late outcomes after propofol maintenance were analysed, the combined NNT for all control event rates was always greater than 9 and, except for late absence of nausea after propofol maintenance, sometimes propofol was not significantly different from control.

### ANALYSIS WITHIN THE RANGE OF 20–60% CONTROL EVENT RATES (TABLE 1, FIG. 1)

Within the 20–60% range of control event rates, the mean incidence of early and late PONV in controls

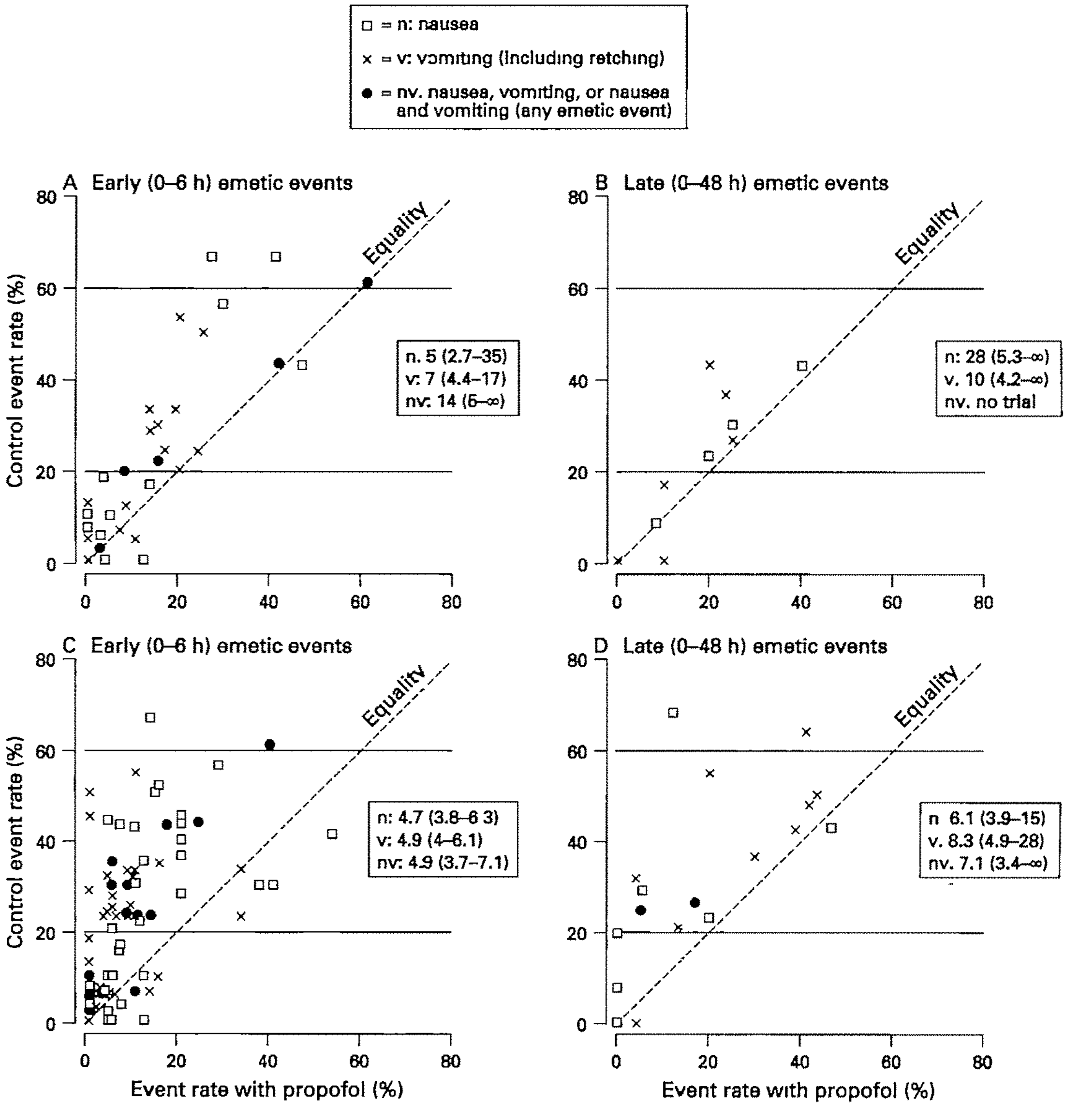

*Figure 1* Early (A, C) and late (B, D) emetic event rates with propofol for induction (A, B) and maintenance (C, D) of anaesthesia compared with other anaesthetics (control). Three different emetic events (see key), both early and late, may be from one study. Only one control arm per study is considered. Horizontal lines indicate a range of control event rates of 20–60%. Values are number-needed-to-treat (95% confidence interval) to prevent an emetic event with propofol within this range. ∞=infinity (absence of a statistically significant difference between propofol and control).

was 36% and 32% when propofol was used for induction, and 33% for both times when propofol was used for maintenance.

Propofol induction (fig. 1A, B) was significantly better than control for absence of both early nausea and vomiting (NNT 5 and 6.7, respectively, each with wide confidence intervals). Absence of any emetic event in the early postoperative period after propofol induction was not significantly different from control. Late outcomes after propofol induction were either not significantly different from control or there were no studies reporting this outcome.

Propofol as a maintenance regimen (fig. 1C, D) was significantly better than control for all early emetic events; point estimates of the NNT to prevent early nausea, vomiting and any emetic event were approximately 5, with confidence intervals ranging from 4 to 7. Prevention of late vomiting and nausea with a propofol maintenance regimen had an NNT of approximately 8 and 6, respectively, both with wide confidence intervals, whereas prevention of late combined emetic events was not significantly different from control.

### SUBGROUP ANALYSIS: TWO DIFFERENT SURGICAL SETTINGS

In 11 studies, propofol maintenance was compared with other anaesthetics in more than 1000 patients undergoing minor gynaecological surgery (abortion, curettage).[41–51] The mean incidence of early vomiting without propofol was 10%; the NNT to prevent early vomiting with propofol was 16 (11–32).

In five studies of 200 patients undergoing major gynaecological surgery, including hysterectomy and laparoscopy,[52–56] the mean incidence of early vomiting in controls was 32%; the NNT to prevent early vomiting with a propofol maintenance regimen compared with other anaesthetics was 4.2 (3–8).

## Discussion

Two of the most recent comprehensive review articles on propofol stated that a significant decrease in PONV was observed with the use of propofol for anaesthesia,[57] and that an increasing body of literature supported the antiemetic activity of propofol.[3] However, very few review articles use valid methods to identify, assess and synthesize information.[58]

The main steps in our approach to propofol and PONV were to identify data systematically and without bias, to define homogeneous subgroups of clinical interest and to use quantitative methods of analysis which allowed sensible statistical and clinical conclusions to be drawn. Further, an arbitrary range of control event rates, excluding studies with very low or very high PONV incidences, enabled analysis of treatment efficacy within a set of data from studies with clinical validity. The lower boundary (control event rate 20%) was set because antiemetic prophylaxis was not considered to be worthwhile when the event rate without treatment was less than 20%. Moreover, in such a setting there would not be enough nausea or vomiting to allow sensitive assay of treatment efficacy. The upper boundary (control event rate 60%) was set because a study which reported an incidence of nausea or vomiting in controls of more than 60% could not be considered as representative of clinical routine. Although a high incidence of vomiting may be reported in particular settings, such as paediatric strabismus surgery,[13] this cannot be regarded as a representative cross-section of clinical reality. Audit has shown that the mean incidence of nausea and vomiting across different surgical settings is approximately 20–40%.[59–62] When control event rates extend beyond this any intervention may become more or less effective and confound the combined results of a meta-analysis.

Within the 20–60% range, mean PONV incidences in controls were similar for early and late outcomes, and for propofol as an induction agent and maintenance regimen. Comparisons of efficacy could, therefore, be made between forms of administration (induction *vs* maintenance) and times (early *vs* late outcomes) without the danger of confounding the results because of different levels of control event rates.

What are the clinically relevant results of this meta-analysis? First, propofol anaesthesia should not be regarded as a universal prophylactic antiemetic if used non-selectively; too many patients would have to be treated with propofol in order to prevent PONV in one of them. A large number of studies and patients in a great variety of clinical settings were analysed; the risk of emetic outcomes without propofol when all studies were included was approximately 22%. This indicates that the data set was a representative cross-section of clinical routine rather than a selected subgroup of high-risk settings. Combined analyses for this data set, regardless of the control event rates, showed a clinically negligible effect of propofol on PONV compared with controls (number-needed-to-treat >5) and sometimes the difference was not statistically significant. These results suggest that it may be inappropriate to expect a beneficial effect of propofol on PONV in every clinical situation.

Second, within the restricted range of control event rates (20–60%) propofol may decrease the incidence of PONV to a clinically relevant extent, but only when given as a maintenance regimen and only in the first few hours after surgery. Even in this setting five patients have to be treated with propofol to prevent early nausea or vomiting in one of them, who would have vomited or been nauseated with another anaesthetic. For late PONV this degree of benefit was lost; despite the same mean control event rate, point estimates of the NNT were higher than for early outcomes and confidence intervals were wide or included no benefit. These results suggest that propofol, when used for maintenance of anaesthesia, may produce a short-lived 20% reduction in vomiting and nauseated patients in a high-risk setting for emesis (i.e. control event rate 20–60%). These results also suggest that the effect of propofol on PONV does not influence long-term patient comfort. It is interesting to note in this connection that late emetic outcomes, although of undoubted importance,[63] were documented in only approximately

25–30% as many patients as early outcomes. This may be because of several factors. Anaesthetists may not be interested in late outcomes and may avoid the increased effort which is needed for prolonged follow-up of patients.

Third, although there is no way from our model to predict an individual patient's outcome with propofol, it may be possible to identify clinical subgroups with higher event rates and a corresponding greater efficacy with propofol. This was shown for paediatric strabismus surgery[13] and confirmed in this study, because women undergoing major gynaecological interventions were much more likely to profit from the effect of propofol on PONV than those undergoing minor gynaecological surgery. Subgroup analysis may enable more rational decision making on how and when to use propofol in a particular group of patients to optimize any potential effect on PONV. This subgroup analysis also demonstrated that it is possible to identify clinical settings where a beneficial effect of propofol on PONV is unlikely.

Fourth, although suggested recently,[64] propofol as an induction agent cannot be regarded as worthwhile prophylaxis for PONV. The efficacy of propofol was either inconsistent or clinically irrelevant for early outcomes and not significantly different from control for late outcomes.

In conclusion, based on data from all published randomized, controlled studies there is evidence that propofol may have a clinically relevant effect on PONV, but only in the short term, when given as a maintenance regimen and when the event rate without prophylaxis is more than 20%. In all other situations—propofol for induction, late outcomes, low control event rates—the difference between propofol and control may be statistically significant but is clinically unimportant. It is over optimistic to expect propofol to act as an antiemetic in every clinical setting, especially if the event rate without prophylaxis is low.

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## Appendix

ANALYSED RANDOMIZED, CONTROLLED STUDIES

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*British Journal of Anaesthesia* 1997; 78: 256–259

# Meta-analytic comparison of prophylactic antiemetic efficacy for postoperative nausea and vomiting: propofol anaesthesia *vs* omitting nitrous oxide *vs* total i.v. anaesthesia with propofol

M. TRAMÈR, A. MOORE AND H. MCQUAY

## Summary

Data from two published and one new meta-analysis were reviewed to compare the antiemetic efficacy of three different anaesthetic regimens: (i) propofol anaesthesia compared with another anaesthetic (control); (ii) anaesthesia without nitrous oxide compared with the same anaesthetic with nitrous oxide (control); (iii) propofol anaesthesia without nitrous oxide (TIVA) compared with another anaesthetic with nitrous oxide (control). Efficacy (prevention of postoperative nausea and vomiting compared with control) was estimated using odds ratio and number-needed-to-treat methods, and compared within a range of 20–60% control event rates for early efficacy (0–6 h) and 40–80% for late efficacy (0–48 h). Propofol anaesthesia or omitting nitrous oxide had similar effects on vomiting, both early and late. Propofol (but not omitting nitrous oxide) decreased the incidence of nausea. TIVA studies were documented poorly; appropriate comparisons with other interventions were not possible. Efficacy of treatments should be compared within a setting-specific range of control event rates. There is insufficient evidence that TIVA with propofol is an anaesthetic technique with a low emetogenic potency. (*Br. J. Anaesth.* 1997; **78**: 256–259).

**Key words**
Anaesthetics i.v., propofol. Vomiting, nausea. Vomiting, antiemetics. Vomiting, incidence. Statistics. Anaesthetics gases, nitrous oxide.

Many pharmacological interventions for preventing postoperative nausea and vomiting (PONV) have been discussed over the past 30 yr.[1–6] The relative efficacy of these interventions is documented poorly and there is no "gold standard". This gold standard would be the most efficacious and least harmful, and increasingly, the cheapest intervention.[7]

In comparing the efficacy of different antiemetic interventions (as opposed to comparing one intervention with a control[8 9]), a new reason for a limited range of control event rates arises. If the efficacy of intervention A has been tested mainly in studies with high control event rates, and intervention B in studies with low control event rates, then intervention A will have more scope for improvement over its control. Therefore, the efficacy of A relative to B would be overestimated.

The choice of upper and lower limits of a restricted band of control event rates for comparing antiemetic efficacy is arbitrary. It should create a band as narrow as possible to reduce the risk of confounding comparisons of estimates of efficacy and should take into account the most likely distribution of event rates without interventions. The compromise is to achieve homogeneity of data but not to exclude too many studies. For this study, both an increased risk of PONV in populations selected for antiemetic studies (and therefore an increased likelihood for high control event rates) and an increase in the cumulative incidence of PONV over time (early *vs* late outcomes) were taken into account.

We defined an appropriate range of control event rates for PONV in which to compare the antiemetic efficacy of three different anaesthetic interventions: propofol maintenance, omitting nitrous oxide and total i.v. anaesthesia (TIVA) with propofol (that is propofol anaesthesia without nitrous oxide).

## Methods

Relevant data were from three separate sources: directly from a published meta-analysis comparing propofol maintenance (intervention) with another anaesthetic (control)[8]; a reworking of a published meta-analysis of anaesthetics without nitrous oxide (intervention) compared with the same anaesthetic but with nitrous oxide (control)[9]; and a new meta-analysis of randomized, controlled studies comparing the antiemetic efficacy of TIVA with propofol (intervention) with another anaesthetic with nitrous oxide (control). Studies for this latter meta-analysis were sought using the same strategy and criteria as previously for the propofol studies (see accompanying article).[8]

For each data set of an intervention the procedure (systematic search of randomized, controlled studies, extraction of PONV data) was essentially the

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same as described previously.[8 9] Three different PONV outcomes were extracted in dichotomous form (i.e. presence or absence of PONV): nausea, vomiting (including retching) and any emetic event (nausea or vomiting). This was done for two time periods: 0–6 h (early PONV) and 0–48 h (late PONV).

Only estimates of efficacy of studies with an early control event rate between 20 and 60% or a late control event rate between 40 and 80% were analysed and compared with each other. These PONV comparator ranges for early and late outcomes were *post hoc* definitions. The early comparator range (20–60% control event rate) was taken from another meta-analysis.[8] The late comparator range (40–80% control event rate) was judged appropriate for the increased late control event rates found in antiemetic studies (unpublished data). Because of the difference between the two ranges, there was no intention to compare early antiemetic efficacy with late antiemetic efficacy.

Statistical significance and clinical relevance of efficacy were evaluated as described in the accompanying article.[8] The main estimate of efficacy was the number-needed-to-treat, which indicated how many patients had to be exposed to an intervention in order to prevent one particular emetic event (nausea, retching/vomiting or any emetic event) in one of them, who would have had this emetic event with the corresponding control treatment.

A statistically significant improvement of an intervention over control was assumed when the upper limit of the 95% confidence interval (CI) of the number-needed-to-treat did not include a negative value (infinity). A significant improvement of one intervention over another intervention was assumed when the 95% CI of the NNT did not overlap, although this is a notably conservative assumption.

Calculations were performed using Excel v 4.0 on a Power Macintosh 7100/66. Tables with data extracted from the analysed reports, including odds ratios with confidence limits, are available from the world-wide-web (http://www.jr2.ox.ac.uk/Bandolier/painres/propponv.html).

## Results

A comparison between TIVA with propofol and a non-propofol–nitrous oxide anaesthetic was found in nine studies[10–18]; in only four were the control event rates within the defined ranges, either early or late.[11 13–15] In all TIVA comparisons the control arm included induction with thiopentone and a maintenance regimen with nitrous oxide and isoflurane, enflurane or halothane.

Relevant data for the two other interventions, propofol maintenance and omitting nitrous oxide, were from a reworking of two previous meta-analyses.[8 9]

### EARLY OUTCOMES (FIG. 1)

The scatter of event rates suggested efficacy in preventing early emetic events with all interventions, especially TIVA.

When data were analysed within the early comparator range (control event rates 20–60%) both propofol for maintenance and omitting nitrous oxide had a similar effect on early vomiting compared with the corresponding control intervention (number-needed-to-treat point estimate approximately 5). Propofol maintenance was as good at preventing early nausea or any emetic event (nausea or vomiting), whereas omitting nitrous oxide was not significantly different from control in preventing early nausea, and prevention of any emetic event was not documented within the comparator range.

Prevention of early vomiting with TIVA showed a tendency for greater efficacy than propofol maintenance or omitting nitrous oxide. However, there were insufficient relevant data with TIVA to allow meaningful comparisons with the other interventions. The analysable TIVA data set within the comparator range was based on 66 treated patients from three small studies reporting vomiting as an early outcome.[11 13 15] The 95% confidence limits of the number-needed-to-treat to prevent early vomiting of all three interventions overlapped. Prevention of early nausea with TIVA, reported within the comparator range in only one study,[14] was not different from propofol maintenance.

### LATE OUTCOMES (FIG. 1)

For all three interventions there was little indication of late efficacy (to 48 h) from the event rate scatters.

Within the late comparator range (control event rates 40–80%) propofol for maintenance and omitting nitrous oxide had the same, statistically significant effect on vomiting. Propofol maintenance showed a favourable effect on late nausea (number-needed-to-treat point estimate approximately 3) but using data from only 38 patients from two small studies with contradictory results. Omitting nitrous oxide had no effect on late nausea. With both interventions prevention of any late emetic event (nausea, vomiting, or nausea and vomiting) was either not significantly different from control (omitting nitrous oxide) or not documented (propofol).

Within the late comparator range, only one TIVA study reported prevention of vomiting as an outcome[15]; late efficacy was not significantly different from a halogenated–nitrous oxide anaesthetic in 25 treated patients.

## Discussion

Quantitative analysis of combined data extracted from systematically searched randomized controlled studies is a powerful test of the evidence that an intervention is efficacious and was used here to try to improve our poor understanding of the relative potency of antiemetic interventions.

Antiemetic efficacy may be identified in a high-risk or low-risk setting. This inequality may confound comparisons between treatments and underlines the necessity of using only studies with comparable underlying risk. Because risk is not well understood in PONV studies we have to rely on the event rate in controls who did not receive an antiemetic treatment. Indeed, we have to assume that there is a close

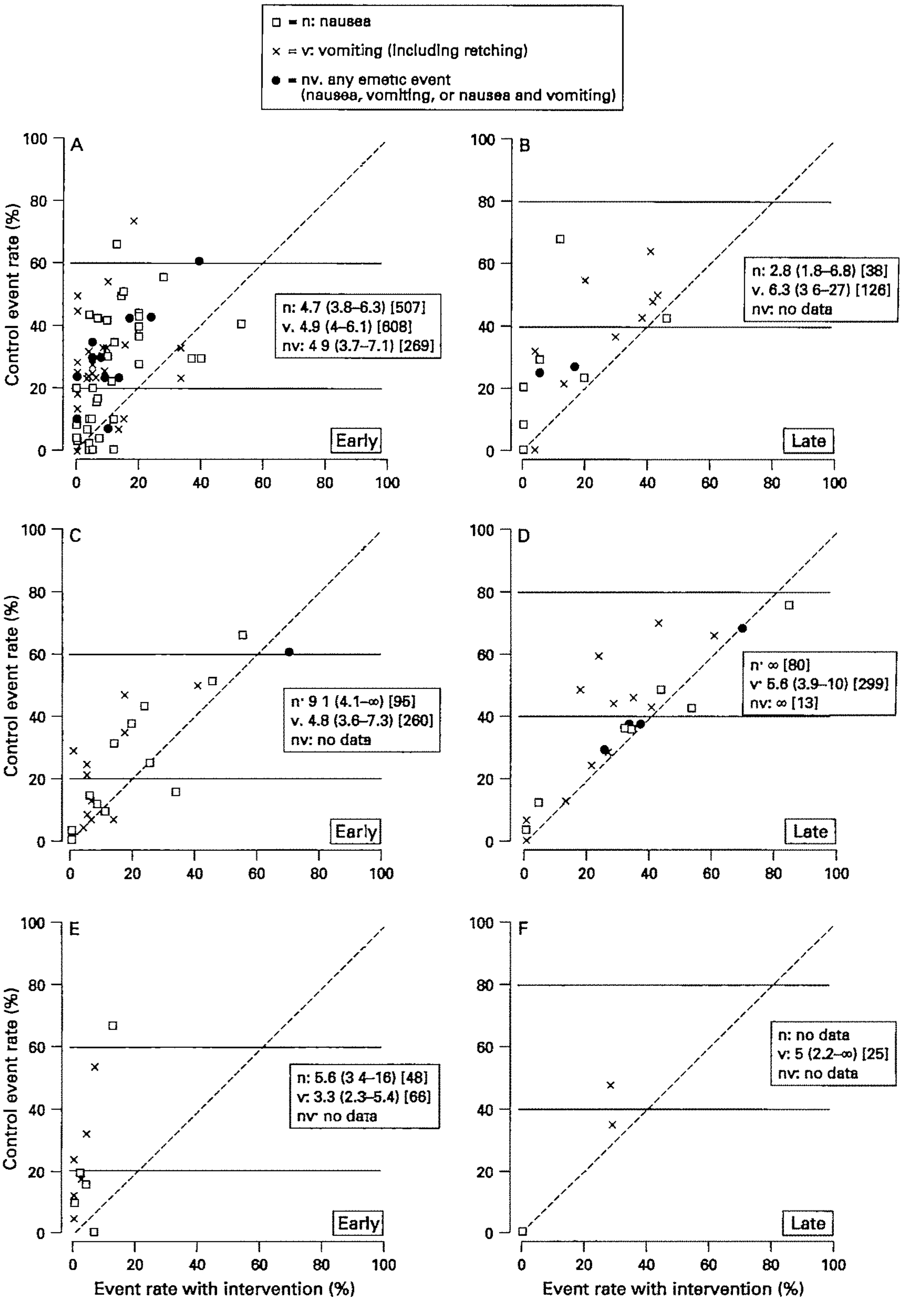

*Figure 1* Early (0–6 h) and late (0–48 h) emetic event rates with: A, B: propofol maintenance (control=another anaesthetic); C, D: omitting nitrous oxide (control=same anaesthetic with nitrous oxide); E, F: total i.v. anaesthesia (control=another anaesthetic with nitrous oxide). Symbols are comparisons between an intervention and control. One study may report 1–3 different emetic events (see key), both early and late. Horizontal lines indicate early (20–60%) and late (40–80%) control event rate comparator ranges. Values are number-needed-to-treat (95% confidence interval) [numbers of treated patients] to prevent an outcome with an intervention compared with control within the comparator range. ∞=Infinity.

relationship between underlying risk and this control event rate and, therefore, we use control event rate as an indicator of risk. We have defined a PONV comparator range of control event rates to evaluate the effect of propofol, as an induction agent or as a maintenance regimen, on early and late PONV.[8] In that study the logic was to eliminate those studies which had little opportunity to show an improvement and those that were clinically irrelevant. In this study the aim was to create a narrow band of control event rates which represented outcomes of the majority of antiemetic studies. Interventions may then be compared on the same basis.

What are the clinically relevant results of this study?

A propofol maintenance anaesthetic and omitting nitrous oxide in general anaesthesia had approximately the same effect on early and late postoperative vomiting. Our model was not designed to compare early with late antiemetic efficacy as in another meta-analysis.[8] However, these results suggest that, even in settings with an extraordinarily high risk of nausea and vomiting (i.e. 40–80% incidence of PONV without prophylaxis), approximately six patients have to be treated with either method to prevent long-term vomiting in one of them. The number-needed-to-treat confidence limits suggested that this number could be twice as high when nitrous oxide is omitted and almost five times as high when propofol is used. Such antiemetic long-term efficacy cannot be regarded as clinically relevant.

Omitting nitrous oxide had no effect on early nausea whereas propofol decreased the incidence of early nausea to the same extent as early vomiting. Prevention of late nausea with propofol maintenance suggested a favourable effect, but from only a few treated patients in two small studies with contradictory results.

Because of the very few studies in the PONV comparator range, TIVA with propofol cannot be recommended based on the present evidence. Even if subsequent studies provided enough data to show a statistically significant and clinically relevant advantage over the two other techniques, there is still the factor that nitrous oxide with propofol reduces the risk of intraoperative awareness[9] and eventually decreases cost.[19 20]

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# A model of the electrocortical effects of general anaesthesia

J. W. SLEIGH AND D. C. GALLETLY

## Summary

In an attempt to describe how reduction in synaptic efficiency by general anaesthetic agents results in loss of consciousness, we examined the behaviour of a two-dimensional (a lattice of 80×80 cellular elements) cellular automaton (CA) computer model as the connectivity between cellular elements was altered. The lattice was taken to represent cortical elements with variable connectivity to their neighbours. The summation of the active elements of the CA lattice was taken to represent a simulated "EEG" signal. If cellular automaton elements had a high probability of connectivity, the simulated EEG showed high frequency predominance and low amplitudes, similar to the desynchronized pattern in an alert person. As connectivity was decreased, median frequency in the simulated EEG decreased and amplitude increased, similar to that in anaesthetized patients. As in our model, we believe it is possible that the human central nervous system in the conscious resting state exists above a critical threshold of synaptic efficiency; awareness is associated with an increase in synaptic efficiency and anaesthesia with a decrease that sharply reduces cortical information transfer. (*Br. J. Anaesth.* 1997; **78**: 260–263).

**Key words**
Anaesthesia, general. Theories of anaesthetic action. Model, computer.

Attempts to explain the mechanisms of action of general anaesthetic agents have concentrated primarily on their effects at the cellular or molecular level.[1–3] In order to understand the mechanisms by which general anaesthetics produce unconsciousness however, it is necessary to link these neurophysiological actions with the resulting disruption that occurs in symbolic information processing or consciousness. In this article we attempt to provide a simple model of cortical EEG activity which illustrates how subtle changes at the neuronal level may result in major and sudden transitions in the global behaviour of the cerebral cortex.

It is unlikely that general anaesthetic action is related to a specific brain site as anaesthesia is a general phenomenon occurring in all life forms to some degree. Similarly, it seems unlikely that general anaesthesia is related to a specific neural effect as it is a property of a wide range of different chemical compounds. Therefore, it is probable that anaesthesia is the final common pathway for a relatively non-specific brain effect.

In recent years, several studies have narrowed down the putative site of action of general anaesthetics.[4] Although the exact mechanisms remain unclear, the perceptual phenomenon of "loss of consciousness" appears closely linked to disruption of cortical association activity.[2] This has been seen electrophysiologically as a decrease in amplitude and an increase in latency in the mid- and long-latency auditory and somatosensory evoked cortical potentials.[5] These appear to be consistent findings that are largely independent of the anaesthetic agent used.[6] Evoked potential studies clearly demonstrate the resistance to anaesthetic action of brain stem processing, relative to that of the cerebral cortex.[7]

Many physical systems are composed of collections of interacting subsystems. The functional output of the whole system at a "macroscopic" level depends almost totally on how these "microscopic" component parts interact. In this field of study a large body of literature has developed that describes how the overall behaviour of a system may change in response to changes in the interactions between the subsystems. It has been observed that dramatic changes (termed phase transitions) at the macroscopic level may occur at certain "critical points" at the microscopic level. A common example of phase transition is the change of a polymer from a sol to a gel form such as happens when cooking an egg. Alterations in the communication or "connectivity" between the individual microscopic elements (the protein molecules) causes a major change in the structure and behaviour of the collective macroscopic system (the egg).

Can we attempt to apply this phase transition model to the phenomenon of general anaesthesia? We suggest that a phase transition resulting in failure of accurate information transmission between spatially separated neuronal assemblies is at least in part an explanation for loss of consciousness. This relatively abrupt phase transition in information transmission is largely concealed behind the relatively continuous smooth changes of EEG

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frequency and amplitude that occur with increasing depth of anaesthesia.

In this article we describe a simple two-dimensional "cellular automaton" model that displays a surprising similarity in behaviour to that of the cerebral cortex, as measured by EEG changes during anaesthesia. The model is similar to the two-dimensional lattice that has been used to describe phase transitions in both the physical sciences[8–10] and ventricular fibrillation in the heart.[11]

## COMPUTER MODEL

A computer program was written in the C language to simulate an 80×80 lattice of units, each of which communicates with its four neighbours (fig. 1). Each unit is capable of passing information or activating its neighbours with a certain probability (the "bond linkage probability" (Pb)). The overall output of the system is defined as the number of active units. This model is similar to the well known "forest fire" model used for describing activity in random resistor networks, polymer bonds and epidemics.[8–10]

The assumptions which relate this model to that of the effects of anaesthetics on cortical function are: (a) it is probable that the cerebral cortex is divided into functional units, each approximately 0.1 $mm^3$ in size.[12] Thus our 80×80 lattice can be thought of as analogous to a two-dimensional surface of cerebral cortex where each unit represents a functional neuronal subsystem; (b) the voltage of the EEG signal is the result of summation of postsynaptic potentials.[13] This might be represented in the model as the total number of active or "depolarized" units in the lattice at any specified time; (c) a major mechanism of action of anaesthetics at the cellular level is to disturb synaptic efficiency in some way.[14] This could be mimicked by a reduction in the probability (Pb) of each unit depolarizing its neighbour. By adjusting values of Pb we could examine the hypothetical effect of a drug which altered synaptic efficiency.

The simulations were implemented on a 40-MHz 486 processor-based microcomputer running under MSDOS, each run lasting approximately 2–5 min.

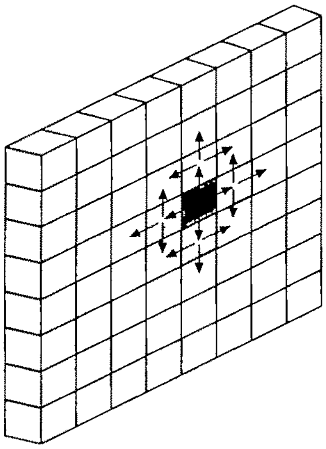

*Figure 1* Visual representation of the spread of activity in the cellular automaton model. Pb is the probability that each cell in the lattice communicates with its neighbour in the direction shown by one of the arrows.

At regular intervals of one time step, an excitatory depolarizing input signal was applied to a random element on one side of the lattice. At each subsequent time step the neighbouring elements became depolarized according to a predefined probability Pb from 0 to 1. Each depolarized site then became refractory to excitation for one time step. This resulted in a wave of activity passing through the lattice. The time taken for the wave to traverse the lattice is known as the percolation time. A short percolation time indicates relatively unimpeded information transfer across the lattice. Conversely, a long percolation time suggests poor information transfer. After an initial period of 500 time steps to reach a steady state, the resultant activity, the "voltage", within the lattice was recorded over time (1000 time steps). We examined this activity over a range of values for Pb. A second simulation was performed in which the excitatory input signal was applied to the empty lattice only when the preceding wave had died out or had reached the opposite side of the lattice. From this simulation 40 percolation times were calculated for each level of Pb. The percentage of percolation times less than 120 time steps (=1.5 lattice size) was chosen arbitrarily as an estimate of the efficiency of information transfer across the lattice and termed the "percolation time index" (PTI).

## PATIENT DATA

For comparative purposes we obtained EEG traces from five, healthy consenting male patients undergoing general anaesthesia for minor surgical procedures. Anaesthesia was induced in each patient with propofol 2–2.5 mg $kg^{-1}$ and fentanyl 100–200 μg, and maintained with 1% isoflurane and 66% nitrous oxide in oxygen. Neuromuscular block was produced with vecuronium as required. Five minutes before induction of anaesthesia and during unstimulated anaesthesia, 30-s epochs of EEG data were recorded from a right occipito-temporal electrode (O2-T4: 10–20 international system). The EEG signal was filtered (low pass 0.3 Hz, high pass 100 Hz), amplified (Grass P511K) and digitized at a sampling rate of 500 Hz using a 14-bit ADC data acquisition unit (Strobes APC, Wellington, NZ). Electrode impedance was less than 5 kΩ. The digitized waveform was transferred to a microcomputer.

These true EEG values were compared with "pseudo EEG data" obtained from the computer simulation with regard to their spectral characteristics.

## Results

Allowing for the relatively small size of the lattice, its observed collective behaviour was similar to results obtained for physical phase transitions.[8]

Data from patients during general anaesthesia showed the well described and expected shifts towards the lower frequencies with induction of anaesthesia; increased power in the delta and theta bands, diminished power in the alpha and beta

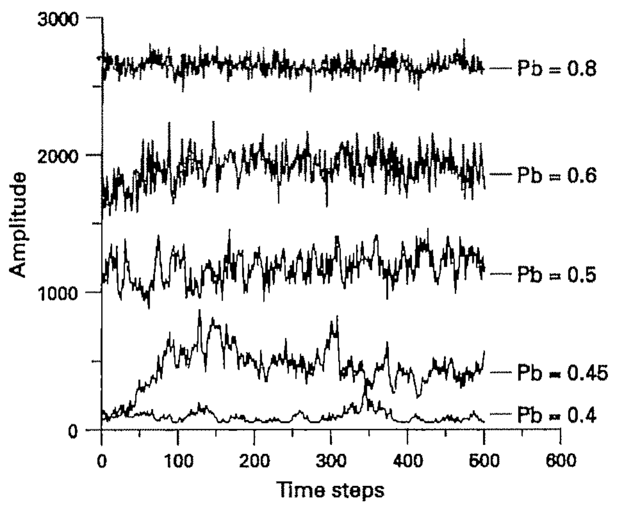

*Figure 2* Typical examples of simulated EEG output from the computer model at various different Pb values. The vertical axis shows absolute amplitude, as measured by the number of active elements at each time step. The horizontal axis is time steps. Unlike true EEG, the signal has not been filtered and therefore represents both AC and DC components.

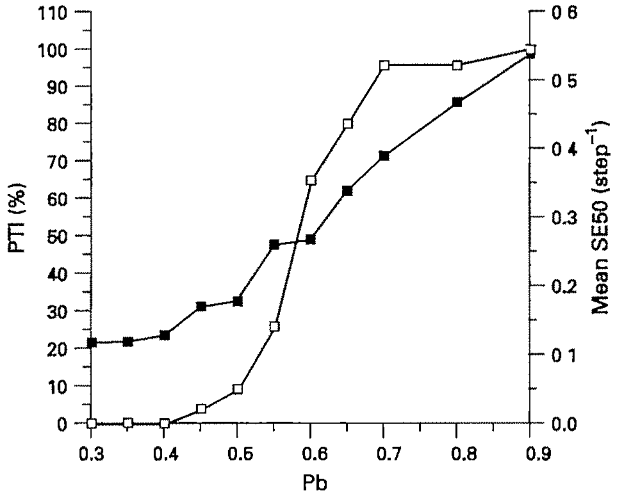

*Figure 3* Mean SE50 (■) and percolation time index (PTI) (□) *vs* Pb values. The SD of the SE50 values was small and relatively constant, ranging from 0.01 to 0.02.

bands and a decrease in spectral edge 50% (SE50).

Activity of the lattice is shown for different Pb values in figure 2. For high (0.8) Pb values (i.e. there was a high probability of a unit depolarizing its neighbouring elements), we observed a low amplitude, high frequency predominance in the power spectrum. As Pb approached the critical value of 0.5, we observed increasing amplitude and lower frequency spectral predominance similar to the EEG data obtained from anaesthetized patients. Below a Pb value of approximately 0.4, forms of intermittency phenomena started to occur with increasing periods of electrical silence interspersed with high amplitude waves. As Pb approached 0.3 the "pseudo EEG" became almost totally silent.

Figure 3 shows the mean SE50 and PTI for the simulations as Pb values were adjusted. The SE50 values are the mean of 10 simulations at each level of Pb. The characteristic feature of SE50 decreasing in a relatively smooth linear manner with decreasing Pb values was similar to the known effects of general anaesthesia.[15] In contrast, cortical information transmission, as estimated by PTI, changed markedly as the critical point was approached. Above the critical point, lattice activity tended to be self-sustaining, whereas below the threshold almost all of the signals rapidly died out.

## Discussion

Attempting to understand how the nervous system processes information without detailed knowledge of specific neural interactions might appear to be an overambitious goal. It is possible, however, that detailed knowledge of the immense complexity of neuronal activity and interactions may not be necessary to understand the essential features of anaesthesia and consciousness.

The activity of our simple cellular automaton model was surprisingly similar to that described for the EEG effects of general anaesthesia. Increasing low frequency activity and reduction of spectral edge occurred smoothly throughout a range of bond linkage probabilities.

The crucial point of the phase transition model is that it relates the abstract notion of information transfer to some measurable output of the system, in this case EEG voltage. Thus when amplitude and wavelength in an EEG increase, it suggests that the rate of information transfer around the cortex has been slowed greatly (fig. 3). Theoretically, as Pb decreases to 0.5, the time for an impulse to traverse the lattice increases rapidly, becoming infinite when Pb <0.5.[8] As a corollary, the best EEG index of awareness is likely to be one that most closely follows the state of information transfer. The SE50, being almost linearly related to Pb, is not very sensitive in this regard and measures that include correlation and time information may be better.

Although the cellular automaton model of phase transition is very general and has been applied to a wide range of different problems, it is consistent with, and complements, a large body of work that suggests that in a state of calm resting, association activity within the cerebral cortex functions above a critical phase transition. Thus cognition of an olfactory input suddenly changes chaotic olfactory cortical activity into regular activity and meaningful behaviour becomes associated with temporal and spatial coherence of the brain's magnetic field.[16 17] It is probable that in the unstimulated state, the complex chaotic dynamics of the central nervous system provides the brain with rich "random" patterns of behaviour from which new adaptive patterns emerge and gives the brain a "flexibility" to respond to external stimuli. The process of arousal, as evidenced by desynchronization of the EEG signal, is thought to be mediated by improved connectivity between neuronal subsystems[12 18 19] just as in our cellular automaton model, which showed that increasing Pb resulted in a less deeply anaesthetized EEG pattern. While anaesthesia may reduce connectivity (i.e. reduced Pb) there is evidence that the profound stimulation of surgery acts to reverse this disconnecting effect.[20 21]

Part of the difficulties with using power spectral EEG analysis to estimate awareness during general anaesthesia is that, for intermediate ranges, the SE50 does not reliably differentiate between awake and unaware patients. It is possible that these subjects are close to the steep part of the phase transition curve (i.e. Pb was close to its critical value). Thus small variation within the population or over time in a single individual results in large changes in cortical information processing (awareness or anaesthesia).

This example demonstrates an important phenomenon associated with phase transitions, that is that the same stimulus can produce completely different effects depending on whether the system is near or far from a critical transition point. This may in part explain conflicting research results which are common in the biological literature.

In summary, we believe that the cellular automaton model provides a useful basis for interpretation of electroencephalographic changes associated with general anaesthesia. Further elaboration of this model may help our understanding of the phenomena of consciousness.

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# Role of vasopressin in the haemodynamic response to laparoscopic cholecystectomy

A. D. WALDER AND A. R. AITKENHEAD

## Summary

We studied 10 patients undergoing laparoscopic cholecystectomy (group 1) and five control patients (group 2). We measured heart rate, arterial pressure, right atrial pressure (RAP), cardiac index (CI), systemic vascular resistance index (SVRI), intrathoracic pressure (ITP), plasma osmolality, adrenaline, noradrenaline and arginine vasopressin (aVP) concentrations, and serum renin activity (SRA), and calculated the atrial transmural pressure gradient (ATPG). We recorded significant decreases in mean arterial pressure (MAP), SVRI and CI in both groups ($P<0.05$) after induction of anaesthesia. MAP and SVRI increased ($P<0.01$) while CI decreased further in group 1 patients during the pneumoperitoneum. In group 1 plasma aVP concentration increased after insufflation of the pneumoperitoneum to a level sufficient to cause the recorded haemodynamic changes. ATPG decreased in group 1 patients during the pneumoperitoneum, and this is a recognized trigger for aVP release. (*Br. J. Anaesth.* 1997; **78**: 264–266).

**Key words**
Surgery, laparoscopy. Hormones, vasopressin. Cardiovascular system, effects.

A large increase in mean arterial pressure (MAP) associated with an increase in systemic vascular resistance index (SVRI) and a reduction in cardiac index (CI) is observed in patients undergoing laparoscopic cholecystectomy.[1–4] This occurs despite the head-up position and increased intra-abdominal pressure which would be expected to decrease venous return of blood to the heart and reduce CI, with a consequent reduction in MAP or its maintenance by a compensatory increase in SVRI. The observed increases in MAP and SVRI are much greater than would be expected from a compensatory response to a reduction in CI, and this infers a direct effect on SVRI. An increase in plasma arginine vasopressin concentration (aVP) has been shown to occur in patients undergoing gynaecological laparoscopy with carbon dioxide pneumoperitoneum,[5 6] and the magnitude of this response is haemodynamically significant.[7] This study was designed to assess the relationship between haemodynamic changes during laparoscopic cholecystectomy and plasma concentrations of aVP.

## Patients and methods

The study was approved by the local Ethics Committee and informed consent was obtained from 18 ASA group I or II patients; 13 were undergoing laparoscopic cholecystectomy (group 1) and five were undergoing minor limb procedures (group 2=control). Inclusion criteria were body weight not more than 20% over ideal weight and no cardiorespiratory disease or medications. All patients received temazepam premedication.

General anaesthesia was induced with propofol 2–3 mg $kg^{-1}$ and maintained with 1–2% isoflurane and 66% nitrous oxide in oxygen. Alfentanil 10 μg $kg^{-1}$ was given before tracheal intubation which was facilitated with vecuronium 0.1 mg $kg^{-1}$. Morphine 0.1 mg $kg^{-1}$ was given for analgesia. Hartmann's solution was infused at 5 ml $kg^{-1}$ $h^{-1}$. Ventilation of the lungs was adjusted to maintain a constant end-tidal carbon dioxide partial pressure of 4.0–4.5 kPa.

Head-up tilt of 15° was set after 10 min (both groups). Pneumoperitoneum was induced in group 1 patients after another 10 min. The carbon dioxide pneumoperitoneum was maintained at 14 mm Hg by an automatic insufflator throughout the laparoscopic procedure.

At the end of surgery residual neuromuscular block was antagonized with neostigmine given with glycopyrronium.

Arterial pressure was measured every 3 min using a Dinamap 1846SX. CI and heart rate were recorded continuously (measured by thoracic electrical bioimpedance using the BoMed NCCOM3-R7 (BoMed Medical Manufacturing Ltd, Irvine, CA, USA)) and averaged over 16 beats. The method used to derive cardiac output has been described previously.[8] Right atrial pressure (RAP) was measured every 5 min after insertion of a central venous catheter after induction. Intrathoracic pressure was measured with a three-channel pressure transducer (Gaeltec CT/G/S3-1, Gaeltec, Dunvegan, Isle of Skye, Scotland) placed in the

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oesophagus 5 cm proximal to the lower oesophageal sphincter and atrial transmural pressure gradient (ATPG) calculated as RAP−ITP. The positions of the CVP and oesophageal catheters were confirmed radiologically using an image intensifier. SVRI was calculated as 80 (MAP−RAP)/CI.

Blood samples were obtained before induction of anaesthesia (T0), 5 min after induction of anaesthesia (T1), 5 min after head-up positioning (T2), 5 min after induction of pneumoperitoneum (T3), after 30 min of pneumoperitoneum (T4) and 5 min after desufflation (T5). In the control group, T3 and T4 were taken as 15 min and 45 min after head-up positioning, respectively, and T5 as 5 min after the end of surgery. Some of the blood from T0, T3 and T5 was analysed for osmolality. All other samples were placed on ice and centrifuged in a refrigerated centrifuge, and the plasma then stored at −40 °C for later analysis for adrenaline, noradrenaline and aVP concentrations, and serum renin activity. Catecholamine concentrations were assayed by high pressure liquid chromatography, and renin activity and aVP by radioimmunoassay.

Differences in the results were assessed using the two sample *t* test with $P<0.05$ considered significantly different.

## Results

Mean ages and weights of the patients were 51 (range 42–63) yr and 72 (SEM 3) kg, respectively, in group 1 and 47 (33–58) yr and 70 (5) kg in group 2. There were five male patients in group 1 and four in group 2.

Three patients were converted from laparoscopic to open cholecystectomy after 18, 22 and 25 min of pneumoperitoneum, respectively, because of technical surgical difficulties. Data from these patients were excluded from analysis.

Changes in haemodynamic variables are shown in tables 1 and 2. There was a significant decrease in MAP, CI and SVRI in both groups of patients after induction of anaesthesia. A significant increase in MAP and SVRI, associated with a further decrease in CI, occurred in group 1 patients after insufflation of the peritoneum. These changes were maintained throughout the duration of the pneumoperitoneum and returned to normal after desufflation. Right

*Table 1* Haemodynamic changes in control patients (mean (SEM)). $^*P<0.05$ compared with value at T0

| | T0 | T1 | T2 | T3 | T4 | T5 |
|---|---|---|---|---|---|---|
| Heart rate (beat min$^{-1}$) | 78 (1) | 80 (1) | 84 (1) | 80 (2) | 77 (2) | 75 (1) |
| MAP (mm Hg) | 88 (2.0) | 77 (3)* | 77 (2)* | 83 (3) | 78 (2)* | 84 (3) |
| RAP (mm Hg) | | 4.1 (0.2) | 4.4 (0.5) | 6.0 (0.3) | 5.3 (0.6) | 5.2 (0.5) |
| CI (litre min$^{-1}$ m$^{-2}$) | 3.4 (0.1) | 2.9 (0.1)* | 2.8 (0.1)* | 3.0 (0.1)* | 3.1 (0.1)* | 3.4 (0.1) |
| SVRI (dyn s cm$^{-5}$ m$^{-2}$ | 2184 (119) | 1804 (101)* | 1832 (98)* | 1927 (109) | 1911 (86) | 2106 (113) |
| ITP (mm Hg) | | 3.3 (0.5) | 3.1 (0.3) | 5.6 (0.4) | 5 2 (0.6) | 3.1 (0.3) |
| ATPG (mm Hg) | | 0.8 (0.2) | 1.3 (0.2) | 0.4 (0.1) | 0.1 (0.2) | 2.1 (0.1) |

*Table 2* Haemodynamic data in laparoscopic cholecystectomy patients (mean (SEM)). $P<0.05$ compared with value at *T0 or †T1

| | T0 | T1 | T2 | T3 | T4 | T5 |
|---|---|---|---|---|---|---|
| Heart rate (beat min$^{-1}$) | 81 (1) | 84 (1) | 83 (1) | 81 (1) | 81 (1) | 80 (1) |
| MAP (mm Hg) | 91 (1) | 78 (1)* | 74 (1)* | 110 (2)*† | 105 (2)*† | 90 (2) |
| RAP (mm Hg) | | 5.1 (0.5) | 4.4 (0.4) | 12.3 (0.5 )† | 10.1 (0.7)† | 7.2 (0 5) |
| CI (litre min$^{-1}$ m$^{-2}$) | 3.5 (0.1) | 2.6 (0.1)* | 2.5 (0.1)* | 2.3 (0.1)*† | 2.3 (0.1)*† | 3.3 (0.1) |
| SVRI (dyn s cm$^{-5}$ m$^{-2}$) | 2148 (93) | 1854 (90)* | 1803 (111)* | 3511 (126)*† | 3677 (98)*† | 2301 (109) |
| ITP (mm Hg) | | 3.2 (0.6) | 1.4 (0.3) | 18.2 (0.4)† | 18.1 (0.3)† | 8.4 (0.4) |
| ATPG (mm Hg) | | 1.9 (0.5) | 3.0 (0.4) | −5.9 (0.5)† | −8.0 (0.2)† | −1.2 (0.2) |

*Table 3* Vasoactive hormone concentrations in control patients (mean (SEM)). No significant differences

| | T0 | T1 | T2 | T3 | T4 | T5 |
|---|---|---|---|---|---|---|
| Adrenaline (nmol litre$^{-1}$) | 0.26 (0.12) | 0.28 (0.14) | 0.42 (0.15) | 0.45 (0.13) | 0.46 (0.16) | 0.39 (0.13) |
| Noradrenaline (nmol litre$^{-1}$) | 0.33 (0.14) | 0.41 (0.12) | 0.46 (0.11) | 0.44 (0.10) | 0.47 (0.12) | 0.43 (0.15) |
| Osmolality (mosmol kg $H_2O^{-1}$) | 284 (1) | | | 284(1) | | 285 (1) |
| Plasma renin activity (ng ml$^{-1}$ h$^{-1}$) | 1.5 (0.3) | 1.8 (0.3) | 2.2 (0.4) | 2.4 (0.4) | 2.0 (0.4) | 2.4 (0.4) |
| Vasopressin (pmol litre$^{-1}$) | 0.8 (0.2) | 0.6 (0.1) | 0.9 (0.2) | 0.8 (0.2) | 1.1 (0.2) | 1.3 (0.3) |

*Table 4* Vasoactive hormone concentrations in group 1 (laparoscopic cholecystectomy) patients (mean (SEM)). $^*P<0.05$ compared with value at T1

| | T0 | T1 | T2 | T3 | T4 | T5 |
|---|---|---|---|---|---|---|
| Adrenaline (nmol litre$^{-1}$) | 0.29 (0.13) | 0.31 (0.14) | 0.52 (0.12) | 0.49 (0.14) | 0.42 (0.16) | 0.32 (0.12) |
| Noradrenaline (nmol litre$^{-1}$) | 0.41 (0.11) | 0.63 (0.20) | 0.74 (0.21) | 0.71 (0.22) | 0.81 (0.24) | 0.72 (0.17) |
| Osmolality (mosmol kg $H_2O^{-1}$) | 285 (1) | | | 285 (1) | | 284 (1) |
| Plasma renin activity (ng ml$^{-1}$ h$^{-1}$) | 1.4 (0.4) | 1.6 (0.4) | 2.3 (0.4) | 2.2 (0.4) | 2.6 (0.4) | 2.5 (0.4) |
| Vasopressin (pmol litre$^{-1}$) | 1.5 (0.5) | 1.4 (0.3) | 3.4 (1.2) | 123 (47)* | 75 (23)* | 32 (6)* |

atrial pressure (RAP) and intrathoracic pressure (ITP) increased in group 1 patients during the pneumoperitoneum, ITP more so than RAP. ATPG decreased during the pneumoperitoneum.

Plasma noradrenaline and adrenaline concentrations, renin activity and serum osmolality did not change significantly in either group.

Plasma aVP concentration did not change significantly during surgery in group 2 patients. In group 1, plasma aVP concentration did not change after induction but increased markedly after insufflation of the peritoneum and remained high after 30 min, decreasing rapidly after desufflation (tables 3, 4).

## Discussion

We found no significant changes in plasma concentrations of adrenaline and noradrenaline, or plasma renin activity in either group of patients. We selected patients undergoing minor peripheral surgery as controls so that the stress response to surgery, and its effects on haemodynamic state, would be minimal and there would be no stimuli from handling or stretching of intra-abdominal viscera.

The reduction in CI and increases in MAP and SVRI have been shown previously in both laparoscopic cholecystectomy and gynaecological laparoscopy.[1–4 9–11] An increase in SVRI with an unchanged or slightly reduced MAP might be expected in patients in the head-up position with increased intra-abdominal pressure as a response to decreased CI secondary to decreased venous return of blood to the heart. The observed increase in SVRI, however, was far greater than would be appropriate for a compensatory mechanism. This suggests that the increase in SVRI is triggered directly, rather than being a feature of compensatory adjustments to other cardiovascular changes.

The marked increase in plasma aVP concentration in patients undergoing laparoscopic cholecystectomy occurred immediately after the pneumoperitoneum was formed and reduced soon after the pneumoperitoneum was released. This temporal relationship and the very high concentrations of aVP recorded have been noted previously in patients undergoing laparoscopy under local anaesthesia.[12]

Release of aVP has been shown to occur in response to an increase in osmolarity, but the maximal response to this stimulus is at a plasma aVP concentration of approximately 10–20 pmol $\text{litre}^{-1}$.[7] Osmolality did not change significantly throughout the study in any of our patients.

The plasma concentrations of aVP in group 1 patients during the pneumoperitoneum have been shown to be associated with significant cardiovascular effects in humans.[7] The typical response to plasma aVP concentrations in excess of 30 pmol $\text{litre}^{-1}$ is increased SVRI and MAP with a decrease in CI.[7] The timing of aVP release in group 1 patients and its magnitude are consistent with a causative action to increase SVRI and MAP and reduce CI.

Traction on abdominal viscera is known to stimulate aVP release,[13] but traction on abdominal viscera during laparoscopic cholecystectomy is not very great. In addition, the plasma aVP concentration increased within 5 min of insufflation with carbon dioxide, but before manipulation of the gallbladder had started.

Decreasing the transmural atrial pressure gradient (more negative intra-atrial pressure or more positive intra-thoracic pressure) has been shown to result in a rapid increase in plasma aVP concentration.[12 14 15] The timing and degree of change in ATPG we recorded were consistent with a triggering action of ATPG on the release of aVP.

In summary, we have shown a marked increase in plasma aVP concentration during pneumoperitoneum in patients undergoing laparoscopic cholecystectomy. The scale of the increase in aVP concentration and its timing are consistent with a causal relationship with recorded increases in SVRI and MAP, and decrease in CI. The observed decrease in ATPG is a likely trigger for aVP release.

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# Pharmacodynamics and pharmacokinetics of rocuronium in intensive care patients†

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**Summary**

We have studied dose requirements, recovery times and pharmacokinetics of rocuronium in 32 intensive care patients. After an initial dose of 50 mg, rocuronium was administered as maintenance doses of 25 mg whenever two responses to train-of-four (TOF) stimulation reappeared (bolus group; $n$=27) or by continuous infusion to maintain one response in the TOF (infusion group; $n$=5). Median requirements for rocuronium were 27.4 (range 14.5–68.3) mg $h^{-1}$ and 43.7 (30.9–50.3) mg $h^{-1}$ in patients in the bolus and infusion groups, respectively. Median total duration of rocuronium administration was 29.0 (12.4–95.5) h and 63.4 (24.0–140.3) h, respectively. Median time from administration of the last bolus dose and end of infusion to recovery of the fourth twitch in the TOF was 100 (45–300) min and 60 (15–155) min, respectively. Arterial blood samples were obtained for up to 10 h after cessation of rocuronium administration, and concentrations of the parent compound and its putative metabolites were measured using high pressure liquid chromatography (HPLC). The plasma concentration profile ($n$=12) was described adequately by a two-compartment model. Mean plasma clearance ($Cl$), steady-state distribution volume ($V^{ss}$), mean residence time (MRT) and elimination half-life ($T_{1/2}{}^{\beta}$) were 3.16 (SD 1.15) ml $kg^{-1}$ $min^{-1}$, 769 (334) ml $kg^{-1}$, 262 (120) min and 337 (163) min, respectively. Recovery times, $V^{ss}$, MRT, and $T_{1/2}{}^{\beta}$ differed from previously published data obtained after rocuronium infusion of moderate duration in surgical patients. (*Br. J. Anaesth.* 1997; **78**: 267–273).

**Key words**
Neuromuscular block, rocuronium. Pharmacodynamics. Pharmacokinetics, rocuronium. Intensive care.

Rocuronium (Org 9426) is a new aminosteroidal, non-depolarizing neuromuscular blocking agent which has an intermediate time course of action and is related chemically to vecuronium (2-morpholino, 3-desacetyl, 16-N-allylpyrrolidino derivative). Several maintenance doses of rocuronium did not result in an increase in duration of action.[1] In surgical patients the pharmacokinetics of rocuronium given as a single bolus dose followed by a continuous infusion have been shown to be similar to those obtained after a single bolus dose.[2–4] The main route of elimination of rocuronium appears to be the hepatobiliary pathway and, unlike vecuronium, rocuronium does not appear to be metabolized in the liver.[5] This may be an advantage of rocuronium in comparison with vecuronium, which has a pharmacologically active 3-OH metabolite. This metabolite is thought to contribute to cumulative characteristics of vecuronium after usual clinical doses given to healthy volunteers[6] and after long-term administration in critically ill patients with concomitant renal failure.[7]

Neuromuscular blocking agents are used occasionally to facilitate mechanical ventilation in intensive care patients, although their use has declined over the past 5 yr,[8] partly because a growing number of reports on delayed recovery from neuromuscular block have appeared.[9 10] One important factor contributing to prolonged neuromuscular block may be absolute and relative overdoses of the neuromuscular blocking agent, which may be attributable to the lack of regular monitoring of the patient's neuromuscular function during drug administration.[11]

This first study of rocuronium in intensive care patients aimed to determine the dose of rocuronium required to facilitate smooth mechanical ventilation in conditions of adequate analgesia and sedation and to ascertain recovery time and pharmacokinetics.

## Patients and methods

We studied 32 patients admitted to the intensive care unit (ICU) because of acute respiratory failure, or multiple trauma or blunt brain trauma, or both, necessitating mechanical ventilation for an anticipated

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period of at least 24 h. After approval by the Ethics Committee of the Medical Faculty at the University of Innsbruck, written informed consent was obtained from the patients' closest relatives or, whenever this was impossible, from the attending intensivist who was not involved in the study. Exclusion criteria were known alcohol or drug abuse, severe hepatic, renal or cardiac disease, neuromuscular disease, pregnancy, age less than 18 or more than 70 yr on admission, and administration of vecuronium within 4 h before the study. On admission, an acute physiological and chronic health evaluation (APACHE) II score and, if applicable, an injury severity score (ISS) were calculated.

In all patients analgesia and sedation were provided by continuous infusion of sufentanil 0.3–1.8 $\mu g\ kg^{-1}\ h^{-1}$ or fentanyl 2–12 $\mu g\ kg^{-1}\ h^{-1}$ and midazolam 0.2–0.8 $mg\ kg^{-1}\ h^{-1}$ to maintain the patient comfortable and free of agitation at any time. Combined parenteral and enteral nutritional support was standardized and included carbohydrates (up to 4 $g\ kg^{-1}\ day^{-1}$), amino acids (up to 2 $g\ kg^{-1}\ day^{-1}$) and lipids (up to 2 $g\ kg^{-1}\ day^{-1}$). Depending on the predisposing disease, other drugs were administered concurrently (i.e. dopamine, dobutamine, phenylephrine, adrenaline, noradrenaline, nitroglycerin, amrinone, frusemide, ranitidine and sucralfate, and antibiotics (ß-lactam antibiotics, aminoglycosides, ciprofloxacin, metronidazole, polymyxin, sulbactam and vancomycin)).

A range of laboratory values, including tests of liver function and calculated creatinine clearance, were obtained daily. Haemodynamic, pulmonary gas exchange and other variables were monitored as part of routine clinical management and were not evaluated further in this study.

### MODES OF ROCURONIUM ADMINISTRATION

Rocuronium was administered i.v. as an initial bolus dose of 50 mg. In 27 of 32 patients (bolus group) neuromuscular block was maintained with repeat doses of rocuronium 25 mg given each time the second response in the indirectly evoked train-of-four (TOF) was detectable by tactile or visual assessment (i.e. approximately 80% neuromuscular block).[12] In the remaining five patients (infusion group) continuous infusion of rocuronium was started at an initial rate of 0.25 $mg\ kg^{-1}\ h^{-1}$ at the time of recovery of the first response in the TOF (T1) after the initial bolus dose. The infusion rate was then adjusted to maintain T1 (i.e. approximately 95% neuromuscular block).[12]

### NEUROMUSCULAR MONITORING

Using a constant-current nerve stimulator (Digistim, Neuro Technology Inc, Houston, TX, USA) in the TOF mode, the ulnar nerve was stimulated at the wrist every 15 min. The number of visual and tactile responses of the thumb was recorded by trained medical students throughout administration of the drug. After cessation of administration of the neuromuscular blocking agent, the time from the last bolus dose and the end of rocuronium infusion, respectively, to the reappearance of all four twitches in the TOF mode was recorded. In addition, in 15 patients the time to attain a TOF ratio of 0.7 was determined by a new neuromuscular transmission monitor based on accelerometry (TOF Guard, Biometer, Denmark), as this device became available in the course of this study.

### PHARMACOKINETICS

In 16 of 32 patients (11 in the bolus group and five in the infusion group) plasma concentrations of rocuronium and its putative metabolites were measured in arterial blood samples. A blank blood sample was obtained either before the first bolus dose or at least 3 days after cessation of rocuronium administration, preferably before the patient was discharged from the ICU. In patients in the bolus group blood samples were obtained approximately every 6 h, just before a repeat dose was administered. In patients receiving rocuronium by continuous infusion, blood samples were obtained at 2, 4, 7, 12, 20, 40 and 60 min after administration of the bolus dose and just before and 1 h after the start of infusion. Furthermore, before and 1 h after a change in the infusion rate, additional samples were obtained. After the last repeat dose, or after cessation of the infusion, samples were obtained at 5, 10, 20, 40, 60, 90, 150, 240, 360, 480 and 600 min. Blood was collected in lithium-heparinized tubes. Plasma was separated within 240 min after withdrawal. Sodium dihydrogen phosphate ($NaH_2PO_4$ 1 mol $litre^{-1}$) solution was added to plasma (0.2 ml of acid to each 1.0 ml of plasma). Samples were stored at −18 °C until analysis.

Concentrations of rocuronium and its potential metabolites, 17-desacetyl-rocuronium (Org 9943) and 16-*N*-desallyl-rocuronium (Org 20860), were measured using high pressure liquid chromatography (HPLC) with 3,17-didesacetyl vecuronium as the internal standard. The precision (reproducibility) of the method was 8% over the range 10–100 000 ng $ml^{-1}$ for rocuronium, 7% over 10–25 000 ng $ml^{-1}$ for 17-desacetyl rocuronium and 12% over 10–25 000 ng $ml^{-1}$ for desallyl rocuronium. The lower limits of detection were 3, 5 and 15 ng for rocuronium, 17-desacetyl rocuronium and desallyl rocuronium, respectively.[13]

The plasma concentration–time data were analysed using the program MultiFit (JH Proost, University Centre for Pharmacy, Groningen, The Netherlands). This program has been used in several pharmacokinetic studies with rocuronium.[2–4] The parameters of a two- and three-exponential function were fitted to the logarithm of the measured plasma concentration, assuming a constant relative error and using the Marquardt algorithm for minimization of the residual sum of squares.[14] Initial estimates of the parameters were obtained from the plasma concentration–time data after the last bolus dose or after the end of the last infusion period. The fitting procedure took into account each plasma concentration measurement and each rocuronium bolus dose administration and, for the infusion group, dose rate, time of start and time of change of each subsequent rocuronium infusion. To test if a three-exponential function fitted better to the data than a two-exponential function, the $F$ test was applied.[15] The volume of the central compartment ($V^c$), steady-state volume of distribution ($V^{ss}$), plasma clearance ($Cl$) and mean residence time (MRT) were calculated using standard equations,[16] assuming that elimination takes place from the central compartment.

STATISTICAL ANALYSIS

Descriptive statistics were applied to patient data, dose requirement for rocuronium, total dose of rocuronium administered, duration of treatment, neuromuscular and kinetic variables. The data were summarized by means of sample size, median, mean (SD), minimum and maximum values. For each patient the mean amount of rocuronium administered per hour was calculated separately. Linear regression analysis was applied to recovery times *vs* duration of treatment, total dose of rocuronium administered, creatinine clearance and tests of liver function (aminotransferases, bilirubin), respectively.

## Results

The 32 intensive care patients (30 males) were given a median APACHE II score of 18 (range 11–39). Median age, weight and height of these patients were 29 (16–65) yr, 80 (60–105) kg and 180 (165–195) cm. Twenty-seven of 32 patients were trauma patients with a median injury severity score (ISS) of 30 (5–59); the remaining five were non-trauma patients. Median creatinine clearance was 110.5 (27.0–186.0) ml min$^{-1}$. Median values for alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities were 22.0 (5–78) iu litre$^{-1}$ and 30.0 (5–93) iu litre$^{-1}$, respectively, and median total bilirubin concentration was 25.1 (3.9–194.4) µmol litre$^{-1}$. Conditions precipitating admission to the intensive care unit are summarized in table 1. Twenty-five of the 32 patients recovered from their illness and were discharged from the ICU at 2–40 days after admission. Of the seven patients (22%) who died because of the severity of their illness, four died within 1 week after administration of rocuronium had been stopped and three died 2–7 weeks later.

*Table 1* Summary of conditions precipitating admission to the ICU. ALI=acute lung injury, ARDS=acute respiratory distress syndrome

| No. of patients | Cause of admission (associated conditions) |
|---|---|
| Trauma patients | |
| 12 | Head trauma + multiple trauma |
| 8 | Multiple trauma |
| 7 | Head trauma |
| Non-trauma patients | |
| 3 | ALI or ARDS (pneumonia, HIV infection; acute necrotizing pancreatitis; empyema of pleura, sepsis) |
| 2 | Acute respiratory failure (heart failure intraoperatively; chronic lung disease) |

PHARMACODYNAMICS

### *Dose requirements, total dose and duration of treatment*

In the 27 patients in the bolus group the median dose of rocuronium required to maintain approximately 80% neuromuscular block was 27.4 (median 14.5–68.3) mg h$^{-1}$ and 0.34 (0.18–0.85) mg kg$^{-1}$ h$^{-1}$, respectively. Median duration of treatment was 29.0 (12.4–95.5) h, and the total dose of rocuronium administered was 875 (375–5775) mg. Evaluation of the amount of rocuronium administered per hour to individual patients revealed a significant time effect, which was investigated further. Dose requirements of rocuronium per hour were fitted to a model using weighted non-linear regression in order to compensate for the decrease with time in the number of patients treated. The dose requirement *vs* time relationship is described by the following equation: mean dose (t)= $0.3793\times 0.5314\times e^{(-0{,}755\times t)}$. From this equation it can be calculated that the mean amount of rocuronium needed for neuromuscular block decreases from 0.63 to 0.38 mg kg$^{-1}$ h$^{-1}$ during the first 6–9 h and remains constant thereafter (fig. 1).

In the five patients in the infusion group one response to TOF (i.e. approximately 95% neuromuscular block) was maintained by a median rocuronium dose of 43.7 (range 30.9–50.3) mg h$^{-1}$ and 0.54 (0.52–0.63) mg kg$^{-1}$ h$^{-1}$, respectively. In this group of patients median duration of treatment was 63.4 (24.0–140.3) h and the total dose administered was 2014 (965–7051) mg. Because of the relatively small number of patients in the infusion group no attempt was made to analyse dose requirements over time as was done in the bolus group.

### *Recovery of neuromuscular function*

Recovery data could not be obtained from all patients because some required further neuromuscular block (with vecuronium or pipecuronium) after the study period. The speed of recovery is summarized in table 2. The total dose of rocuronium administered, duration of treatment (fig. 2) and creatinine clearance and tests of liver function (ALT,

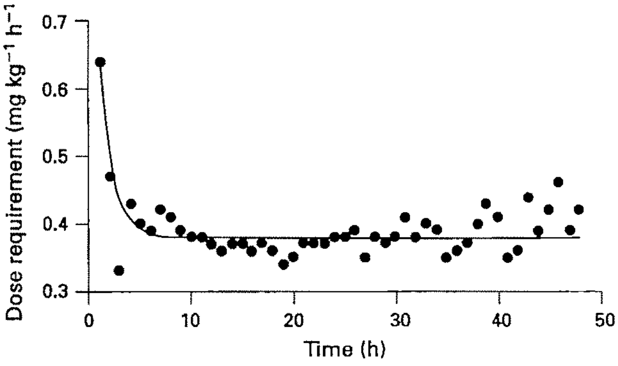

*Figure 1* Mean dose of rocuronium (●) administered to patients in the bolus group ($n$=27) during the first 48 h and estimated relationship between dose and time (represented by the solid line).

*Table 2* Summary of recovery characteristics after administration of the last bolus dose of rocuronium and after cessation of rocuronium infusion, respectively (median (range)). Time to T4=Time until presence of fourth response in TOF; time from T1 to T4=time between reappearance of the first and fourth response in TOF; time from T4 to TOF 0.7=time between reappearance of the fourth response to TOF and attainment of T4/T1 ratio of 0.7. NA=Not applicable

| | *n* | Bolus | *n* | Infusion |
|---|---|---|---|---|
| Time from last bolus to T4 (min) | 19 | 100 (45–300) | | NA |
| Time from end of infusion to T4 (min) | | NA | 5 | 60 (15–155) |
| Time from T1 to T4 (min) | 19 | 50 (30–145) | 5 | 60 (15–155) |
| Time from T4 to TOF 0.7 (min) | 10 | 115 (40–220) | 5 | 125 (75–440) |

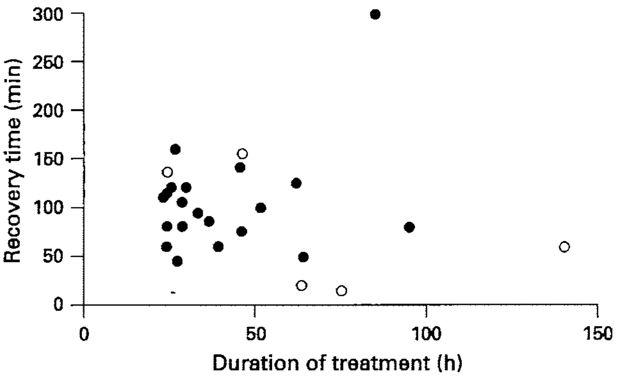

*Figure 2* Recovery time, that is time to reappearance of the fourth response in the TOF after the last bolus dose (●) or the end of infusion (○) *vs* duration of treatment.

AST, bilirubin) did not reveal any significant correlation with time to recovery of T4 (i.e. four responses of the thumb to TOF stimulation) after the end of rocuronium administration. In 15 patients recovery of the T4/T1 ratio was obtained. In these patients mean plasma concentration of rocuronium at a TOF ratio of 0.7 was 870 (SD 460) [range 430–1830] μg litre$^{-1}$.

PHARMACOKINETICS

Plasma samples of 16 patients were available for pharmacokinetic analysis. Four of these patients could not be included in the summary statistics of pharmacokinetic variables because of insufficient sampling (one patient) or unreliable estimates of the calculated variable because of a large residual coefficient of variation. In the final analysis the outcome of the two-exponential fit was preferred. In this study, the mean residual coefficient of variation (cv) was 16% (range 10–26%), which is not markedly higher than the measurement error in the rocuronium plasma concentration assay (10–15%). In general, standard errors of estimated individual pharmacokinetic variables were relatively small; the mean value of the relative standard error was 5 (range 2–17) % for clearance, 28 (8–66) % for $V^c$, 14 (7–38) % for $V^{ss}$, 11 (5–23) % for MRT and 19 (5–38) % for terminal half-life. The main pharmacokinetic variables in the bolus ($n$=8) and infusion ($n$=4) groups are summarized in table 3 together with data from two previous studies in surgical patients where rocuronium was administered as a single bolus dose followed by continuous infusion to maintain 90% neuromuscular block for a period of approximately 2 h.[2 3]

## Discussion

Knowledge of pharmacodynamics and pharmacokinetics of neuromuscular blocking agents acquired in the course of studies in surgical patients, who were given rather small doses during a short period, may not be directly applied to intensive care patients. This consideration is supported by the main findings of this first study on effect-controlled administration of rocuronium in intensive care patients.

First, the dose required to maintain neuromuscular block decreased during the first 6–9 h and remained constant thereafter. Second, recovery time after administration of rocuronium for more than 24 h was prolonged moderately in comparison with administration up to 3 h in surgical patients. Third, in intensive care patients the volume of distribution at steady state was increased and terminal half-life

*Table 3* Main pharmacokinetic variables of rocuronium obtained from ICU patients (bolus and infusion) in the present study, and from two previous studies in surgical patients after rocuronium infusion of moderate duration (mean (SD) [range]; unless otherwise stated). $V^{ss}$ (ml kg$^{-1}$)=Volume of distribution at steady state; $T_{1/2}{}^{\beta}$ (min)=terminal half-life; *Cl* (ml kg$^{-1}$ min$^{-1}$)=clearance; MRT (min)=mean residence time (*Data from Sparr, Khuenl-Brady and Eriksson[2]; **data from McCoy and colleagues[3])

| | ICU patients ($n$=12) | Surgical patients (i.v. anaesthesia; $n$=7)* | Surgical patients (halothane anaesthesia; $n$=8)** |
|---|---|---|---|
| Median duration of rocuronium administration (h) | 39.38 | 2.16 | 1.23 |
| Median total dose (mg) | 937.5 | 195.7 | 67.0 |
| *Cl* (ml kg$^{-1}$min$^{-1}$) | 3.16 (1.15) [1.39-5.07] | 4.50 (1.95) [2.80-8.61] | 3.30 (0.77) [1.97-4.55] |
| $V^c$ (ml kg$^{-1}$) | 160 (88) [40-291] | 146 (56) [71-238] | 62 (8) [48-71] |
| $V^{ss}$ (ml kg$^{-1}$) | 769 (334) [314-1351] | 310 (80) [205-408] | 213 (40) [152-303] |
| MRT (min) | 262 (120) [89-460] | 78 (36) [41-132] | 67 (19) [47-97] |
| $T_{1/2}{}^{\beta}$ (min) | 337 (163) [125-686] | 108 (37) [64-163] | 86 (18) [54-109] |

and mean residence time were prolonged compared with surgical patients with normal hepatic and renal function who received rocuronium for an intermediate duration.

A median dose of rocuronium of 27.4 mg $h^{-1}$ administered to patients in the bolus group was sufficient for smooth mechanical ventilation in ICU patients under adequate sedation and analgesia. In patients in the bolus group the next maintenance dose was not given before the second response in the TOF had reappeared. It occurred several times that three responses to TOF stimulation were detectable when the next bolus dose was given. Mean neuromuscular block in the bolus group was therefore approximately 80%.[12] Higher doses of rocuronium were administered to patients in the infusion group to maintain one response to TOF stimulation (i.e. 95% neuromuscular block). The median dose requirement in the infusion group (43.7 mg $h^{-1}$) in this study was comparable with that necessary in surgical patients for 90% neuromuscular block under i.v. anaesthesia.[2 17 18]

In patients in the bolus group, evaluation of dose requirements for rocuronium over time revealed a significant time effect (fig. 1). In addition, the doses of rocuronium administered to patients in both groups differed greatly from case to case. Therefore, monitoring of neuromuscular function is mandatory in ICU patients in order to adjust the dose to the individual needs of each patient and to avoid overdosing. Monitoring of neuromuscular function, however, does not eliminate prolonged weakness and myopathy in intensive care patients receiving neuromuscular blocking agents.[10 19] The results of this study suggest that a block of approximately 80%, which corresponds to that provided in the bolus group, may be sufficient to facilitate mechanical ventilation under adequate sedation and analgesia, even though some of the patients needed high levels of positive end-expiratory pressure and inversed-ratio ventilation for appropriate oxygenation. If, however, full relaxation of the diaphragm is desired, additional doses of rocuronium may be necessary to establish complete neuromuscular block of the diaphragm,[20] for example to prevent coughing on tracheal suction in patients with severe head injury.[21] The optimal level of neuromuscular block and the mode of administration of neuromuscular blocking agent (repeated bolus injections or continuous infusion) should be adapted to the individual needs of ICU patients.

None of the patients receiving rocuronium in this study showed prolonged recovery from neuromuscular block, if the definition given by Segredo and colleagues[7] is applied (i.e. failure to recover any response to ulnar nerve stimulation within 2 h after administration of the last dose of a neuromuscular blocking agent). However, recovery of neuromuscular function was moderately delayed in ICU patients compared with surgical patients who received an infusion of rocuronium for up to 3 h duration.[2 22] In this study recovery time was not related to the total dose of rocuronium given, duration of treatment, creatinine clearance or tests of liver function (aminotransferases, bilirubin). In 47% of patients in this study the time to attain a T4/T1 ratio of 0.7 was assessed using a small accelerometer (TOF Guard) designed for routine monitoring. The validity of TOF values obtained in the ICU setting using this device has not been investigated. In surgical patients, however, it was demonstrated that the limits of agreement are wide between TOF values obtained using this particular acceleration monitor and a mechanomyographic monitor, which is why these two monitoring systems should not be used interchangeably.[23]

In this study the pharmacokinetic variables of individual patients of both groups were analysed together, as the two different modes of rocuronium administration (single bolus dose *vs* continuous infusion) were not expected to produce different results. None of the putative metabolites of rocuronium was detected in any of the patients. In most subjects, the plasma concentration profile followed a two-exponential decay after the end of rocuronium administration, and no sign of non-linear kinetics were observed. However, in intensive care patients it is questionable if processes of drug distribution and elimination are linear and invariable in time. Therefore, the pharmacokinetics can be described only in global terms. It may be of more importance to take into account intra-individual variability as a result of (patho-) physiological changes such as diurnal rhythms, changes in organ perfusion and organ function, changes in the ratio between extra- and intravascular fluid content, and number of receptors. Up-regulation of receptors may lead theoretically to an increased level of rocuronium necessary to achieve the same degree of neuromuscular block. In this study there was no evidence of resistance to rocuronium, as the requirement for rocuronium was constant after more than 6–9 h of administration. Concomitantly administered drugs may interfere with the pharmacodynamics of rocuronium and possibly also with drug clearance.

The main pharmacokinetic variables of rocuronium in ICU patients were different compared with surgical patients,[2 3] that is volume of distribution at steady state was increased, plasma clearance was decreased and terminal half-life and mean residence time were prolonged. These pharmacokinetic variables may differ because of true differences between ICU and surgical patients. Clearance, for example, might be diminished as a result of impaired renal or hepatic function. Differences in pharmacokinetic variables may, however, be artefacts and result from differences in total duration of administration, total dose, plasma concentrations and sampling schedule. Plasma concentrations during the terminal phase were markedly higher after long-term administration, either by infusion or by repeated bolus doses, than after short-term administration. Therefore, plasma concentrations remained above the limit of quantification much longer than after short-term administration. As a result, the apparent half-life may be longer, even if the "true" half-life is similar. Consequently, the calculated volume of distribution at steady state also increased, and the calculated plasma clearance decreased.

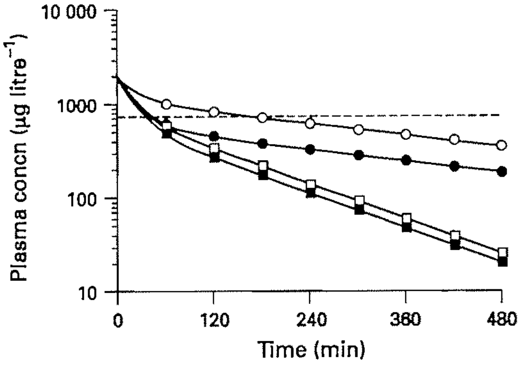

*Figure 3* Simulation of the plasma concentration profile of rocuronium after stopping a BET infusion producing a constant plasma concentration of 2000 μg litre$^{-1}$ over a period of 2 h (closed symbols) and 40 h (open symbols) in ICU patients (○, ●) and surgical patients (□, ■), respectively. The dashed line at 750 μg litre$^{-1}$ indicates the level at which 10% neuromuscular block was reached.

## Appendix

In order to investigate the consequences of the differences in drug disposition between ICU and surgical patients, the time course of the plasma concentration profile was simulated for both types of patients To clarify the influence of duration of drug administration, the plasma concentration was simulated after stopping an infusion lasting 2 and 40 h, respectively (fig. 3). These time values were chosen because they represent typical values of the duration of a rocuronium infusion in surgical patients[2 3]and in the ICU patients in this study, respectively.

For surgical patients the pharmacokinetic data of rocuronium were derived from a study in which rocuronium was administered as a bolus dose of 600 μg kg$^{-1}$ followed by a continuous infusion to maintain twitch height at 10% of control.[2] The mean pharmacokinetic variables of a two-exponential model were: clearance 4.51 ml kg$^{-1}$ min$^{-1}$, intercompartmental clearance 1.77 ml kg$^{-1}$ min$^{-1}$, $V^{c}$ 146 ml kg$^{-1}$ and $V^{ss}$ 310 ml kg$^{-1}$.

For ICU patients the mean pharmacokinetic data of this study were used.

For both types of patients the plasma concentration profile was maintained at a constant level of 2000 μg litre$^{-1}$ by means of bolus administration followed by an infusion with a continuously decreasing infusion rate according to the BET scheme.[24] After 2 and 40 h, respectively, the infusion rate was stopped, and the plasma concentration profile was followed for 8 h.

The plasma concentration profiles after stopping the infusion are depicted in figure 3. After 2 h of infusion, the plasma concentration decay in ICU patients was less rapid than that in surgical patients. However, the decay over the concentration range from 2000 to 750 μg litre$^{-1}$, which corresponds to approximately 90% and 10% neuromuscular block, was only slightly retarded in the ICU patients compared with the surgical patients.

In contrast, after 40 h of infusion, the decay after stopping the infusion was much slower in the ICU patients, and the time necessary to reach 750 μg litre$^{-1}$, or 90% recovery, was 160 min compared with 40 min in surgical patients. Simulations over a longer period of time resulted in approximately the same profiles as shown in figure 3, indicating that steady state had been reached.

As shown by the simulations, both duration of treatment and altered pharmacokinetics may be responsible for the alteration in the recovery profile in ICU patients compared with surgical patients.

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# Predominant involvement of motor fibres in patients with critical illness polyneuropathy

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## Summary

Critical illness polyneuropathy (CIP) is a recognized cause of muscle weakness and failure of weaning from a ventilator. In order to characterize the features of CIP, we have examined 28 consecutive surgical patients with severe sepsis using bedside electrophysiology. Of the 28 patients (median APACHE II score 31), 20 developed moderate to severe CIP, as shown by the presence of moderate to severe denervation activity on resting EMG. The median nerve compound muscle action potential (CMAP) amplitudes were reduced to 3.24 (SEM 0.48) mV, while sensory nerve action potential (SNAP) amplitudes obtained from the same nerve were normal (13.1 (1.9) μV). In approximately 50% of these patients, the reduction in CMAP exceeded 50% of the lower limit of normal. Similar results were obtained from stimulation of the ulnar nerve. We conclude that CIP is a major complication in patients with severe sepsis and prolonged artificial ventilation. It predominantly involves motor fibres and thus markedly interferes with weaning from the ventilator. (*Br. J. Anaesth.* 1997; **78**: 274–278).

**Key words**
Complications, critical illness polyneuropathy. Intensive care. Complications, sepsis.

In recent years, an acute and often severe axonal polyneuropathy has been recognized as a complication of sepsis and multiple organ failure.[1 2] Electrodiagnostically, this condition, termed critical illness polyneuropathy (CIP), has been found in up to 70% of patients suffering from sepsis or multiple organ failure.[3] The clinical features include flaccid quadriplegia, hyporeflexia and muscular atrophy. Difficulty in weaning affected patients from the ventilator prolongs stay in the intensive care unit (ICU) and increases morbidity and mortality. Involvement of both sensory and motor nerve fibres has been suggested,[4 5] although clinically the motor syndrome predominates. The purpose of this study was to further characterize the features of CIP using electrophysiology.

## Patients and methods

After obtaining institutional Ethics Committee approval and informed consent from each patient's next of kin, we studied 28 surgical patients from our ICU who had evidence of sepsis and required prolonged mechanical ventilation. Seven additional patients with a previous history of neuromuscular disease, diabetes mellitus, uraemia or alcoholic liver disease were excluded. Sepsis was defined according to the criteria of the ACCP/SCCM.[6] All patients underwent neurological examination and electrodiagnostic studies at the bedside using a Dantec Cantata instrument (Dantec Inc., Copenhagen, Denmark). Data were obtained on days 5–7 after the onset of mechanical ventilation, and repeated weekly within the first month and on a 2-week schedule over the next 2 months. Thereafter, a 3-week schedule was used if the patient was still in the ICU.

For sensory measurements, antidromic recordings were made from the median nerve using ring electrodes and from the sural nerve using needle electrodes. For each measurement, 20 responses were averaged. Compound muscle action potentials (CMAP) were recorded with surface electrodes from the abductor pollicis brevis muscle after supramaximal stimulation of the median nerve at the wrist and elbow. Similarly, the ulnar, peroneal and tibial nerves were stimulated, and responses were recorded from the abductor digiti minimi and the abductor hallucis muscles, respectively (table 1). Amplitudes of the compound action potentials were measured as the maximum peak-to-peak voltage after distal stimulation. Nerve conduction velocity was determined according to standard procedures.[7] At least one proximal and one distal arm muscle were examined by needle electromyography (EMG). Abnormal spontaneous activity, as shown by the presence of fibrillation potentials and positive sharp waves in resting muscles, was graded on a scale of 0–3, where 0 is normal, 1 mild, 2 moderate and 3 severe.[5 8] Patients with grade 2 and 3 denervations were considered to have definite CIP severe enough to cause or contribute to weaning failure, and those

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*Table 1* Nerve conduction studies performed in 28 patients with critical illness

| Nerve | Stimulation site<br>Distal | <br>Proximal | Recording site |
|---|---|---|---|
| Median | | | |
| Motor | Wrist | Elbow | Abductor pollicis brevis muscle |
| Sensory | Wrist | Elbow | Second digit |
| Ulnar | | | |
| Motor | Wrist | Elbow | Abductor digiti minimi muscle |
| Sensory | Wrist | Elbow | Fifth digit |
| Tibial | Ankle | Knee | Abductor hallucis muscle |
| Peroneal | Distal tibia | Below head of fibula | Extensor digitorum brevis muscle |
| Sural | Dorsal aspect of the calf | | Lateral ankle |

with grade 1 denervations were deemed to have mild neuropathy that would not account substantially for weaning failure. Neuromuscular transmission was assessed by repetitive stimulations at 3 and 30 Hz. Vitamins, including thiamine, pyridoxine and cobalamin, were administered generously, starting early in the disease course. Serum concentrations of electrolytes, including phosphate and magnesium, were measured repeatedly and maintained within the normal range by frequent i.v. supplementation. Neuromuscular blocking agents were given only infrequently and on an intermittent basis. Results are given as mean (SEM).

*Table 2* Clinical data of 28 study patients (median (range) or number). *Seven of these patients died within the first 2 weeks after admission, the remaining patient died on day 24

| | |
|---|---|
| Sex (M/F) (*n*) | 19/9 |
| Age (yr) | 70 (16–80) |
| Primary illness | |
| General surgery | 5 |
| Cardiac surgery | 15 |
| Neurological | 3 |
| Trauma | 5 |
| APACHE II score on admission | 31 (23–38) |
| Duration of mechanical ventilation (days) | |
| All patients | 29.5 (7–143) |
| Survivors | 35 (9–84) |
| Non-survivors | 23.5 (7–143) |
| Deaths (*n*) | 18 (64%) |
| Serum creatine kinase (*n*=23) | |
| Normal (*n*) | 15 |
| Increased (*n*) | 8 |
| Critical illness polyneuropathy (*n*) | |
| Moderate to severe | 20 (71%) |
| None or slight | 8 (28%)* |

## Results

We studied 28 patients, aged 16–80 yr (table 2). Median APACHE II score was 31 (range 23–38, 10 survivors). Eighteen of these patients died 7–143 days after admission to the ICU. The 10 survivors were weaned from the ventilator within 9–84 days after initiation of mechanical ventilation.

Of the 28 patients, 20 developed grade 2–3 denervation potentials on resting EMG (fig. 1). Median time to develop grade 2 to 3 denervations was 21 days after admission to the ICU, with the earliest occurrence of grade 1 denervations on day 8 and grade 2 denervations on day 11. In a patient admitted because of sepsis, grade 3 denervations were already present at the initial examination on day 4. Of the eight patients who had no or only few denervation potentials, seven died within the first 2 weeks and the remaining patient died on day 24. On neurography, there were normal or near-normal conduction velocities and distal latencies in all patients (table 3).

In the 20 patients with grade 2 and 3 denervations, CMAP amplitudes of the median nerve were

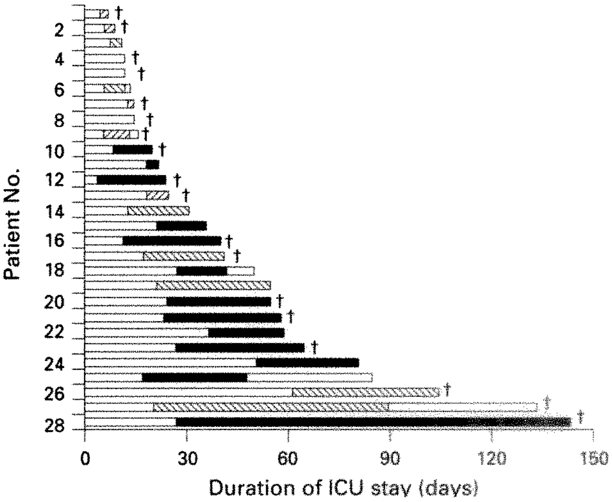

*Figure 1* Duration of mechanical ventilation, electrophysiological status and outcome of the 28 study patients. ▨=Patients with CMAP amplitudes ≤5 mV, ▧=patients with CIP and normal CMAP amplitudes, ■=patients with CIP and CMAP amplitudes ≤5 mV, □=patients without CIP and normal CMAP amplitudes. †Patient died.

*Table 3* Neurographic data (mean (SEM)) of 20 patients with critical illness polyneuropathy. CMAP=compound muscle action potential; SNAP=sensory nerve action potential. [Upper and lower limits of normal]

| Nerve | Velocity ($m\ s^{-1}$) | Distal motor latency (ms) | CMAP (mV)<br>SNAP (μV) |
|---|---|---|---|
| Median, motor | 49.7 (1.4) [>48.0] | 4.5 (0.1) [<4.2] | 3.24 (0.48) [>5.0] |
| (CMAP ≤50% of normal, *n*=12) | 46.8 (1.9) | 4.6 (0.2) | 1.13 (0.21) |
| Median, sensory | 45.3 (1.1) [>49.0] | — | 13.1 (1.9) [>12.0] |
| (CMAP ≤50% of normal, *n*=12) | 45.1 (1.6) | | 11.8 (2.3) |
| Ulnar, motor | 55.1 (3.1) [>47.0] | 3.9 (0.2) [<3.9] | 4.3 (1.0) [>5.2] |
| Ulnar, sensory | 40.9 (2.5) [>50.5] | — | 18.5 (5.7) [>10.5] |
| Tibial | 40.7 (1.1) [>41.0] | 5.4 (0.2) [<5.5] | 5.4 (0.9) [>5.2] |
| Sural | 43.3 (2.0) [>40.0] | — | 5.6 (1.3) [>5.0] |
| Peroneal | 42.9 (1.1) [>41.0] | 6.1 (0.3) [<5.0] | 2.6 (0.57) [>4.5] |

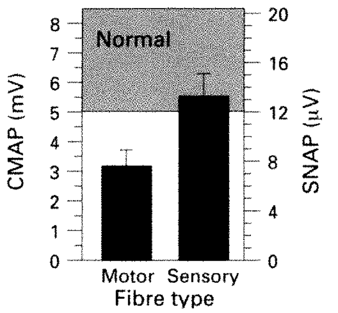

*Figure 2* Compound muscle (CMAP) and sensory nerve (SNAP) action potential amplitudes after supramaximal stimulation of the median nerve in 20 patients with sepsis and prolonged mechanical ventilation.

reduced to 3.24 (SEM 0.48) mV, while sensory nerve action potential (SNAP) amplitudes from this nerve were normal (fig. 2). In 12 of these patients, median nerve CMAP amplitudes were less than 50% of the lower limit of normal, ranging from only 57 µV to 1.84 mV, while median nerve SNAP amplitudes were not significantly reduced. An additional five patients with no or only grade 1 denervations also had decreased median nerve CMAP and normal SNAP. These five patients died early during the disease. Similar results were obtained from the ulnar and peroneal nerves, while CMAP from stimulation of the tibial nerve were not significantly reduced. Sural nerve action potentials were normal. Repetitive stimulation studies with short and long runs were found to be normal in all patients. None of the patients had features of demyelination that would indicate a far worse diagnosis.[9]

Serum creatine kinase (CK) concentrations from 23 patients were normal in 15 and slightly increased in eight. The highest CK concentrations were found in a patient with multiple trauma (477 iu litre$^{-1}$; normal <80 iu litre$^{-1}$). Two patients underwent muscle biopsy which revealed neurogenic changes and slight myopathy, preferentially affecting type II fibres. Lumbar puncture was performed in four patients and revealed no abnormalities. Clinically, most patients developed generalized and marked muscular atrophy during their stay in the ICU. On palpation, the musculature gave a peculiar soft and pasty impression. As far as patients could be examined, they were found to have severe flaccid tetraparesis. Sensory testing was impossible because of sedation or encephalopathy in the majority of patients. In most patients, tendon reflexes were decreased but present, even in those with severe CIP.

## Discussion

Of the 28 patients in this study, 20 (71%) developed moderate to severe CIP according to the EMG results. On neurography, these 20 patients had abnormal CMAP and normal SNAP from stimulation of the median and ulnar nerves. Similarly, peroneal CMAP were reduced while sural SNAP were normal. This discrepancy between motor and sensory amplitudes was consistent in repeated examinations. In approximately 50% of these patients, the discrepancy was particularly evident. This finding indicates a predominant involvement of motor nerves by CIP and suggests that weaning from the ventilator may not be possible in individual patients with severe CIP. Thus forced weaning manoeuvres may endanger these patients unnecessarily. Bedside electrophysiological studies should aid in early recognition of CIP and monitoring of its course. Such a strategy may allow a rational approach to be adopted when weaning septic patients from the ventilator. The reason why tibial CMAP were not reduced significantly is not known; it is not clear if this indicates a predilection of CIP for specific nerves.

There is some evidence from the literature that CIP affects motor fibres to a greater extent than sensory fibres. In Bolton and colleagues' original series, patients with CIP demonstrated decreased motor amplitudes to 30% of control levels at the nadir of the illness, while sensory amplitudes reached 60% of control levels.[10] In contrast, in patients with Guillain–Barré syndrome, the amplitudes of both fibre types were depressed to equally low levels (25% of control). Coakley and colleagues described a motor axonal syndrome in three patients undergoing mechanical ventilation for obstructive pulmonary disease, two with complete absence of any sensory involvement.[11] In another series, 12 of 27 patients showed normal SNAP but abnormal CMAP amplitudes,[12] and similar findings have been observed by others.[2 13–15] Moreover, several sural nerve biopsies obtained at the time of severe muscle wasting showed no signs of axonal degeneration.[2 14]

The selective decrease in CMAP amplitudes raises the question of disturbed neuromuscular transmission, myopathy, lesions to the anterior horn cells and the motor variant of Guillain–Barré syndrome.[16] Prolonged neuromuscular block has been observed in patients treated with high doses of non-depolarizing neuromuscular blocking agents (for review, see Watling and Dasta[17]). However, in most CIP series, including our study, such agents were administered only infrequently and in low doses.[2 3 11] Moreover, repetitive nerve stimulations in our patients and in others[4 18] provided no evidence of disturbance at the neuromuscular junction.

Different types of myopathy have been described with increasing frequency in ICU patients. In a subgroup, necrosis of myofibres occurs, provisionally termed "necrotizing myopathy of intensive care".[19–21] Such patients are frequently admitted for acute severe asthma, have markedly increased CK concentrations, are generally non-septic and have received high-dose steroids, non-depolarizing neuromuscular blocking agents, or both.[22] Other ICU patients with acute myopathy do not develop significant increases in serum CK concentrations, and muscle biopsy does not reveal widespread necrosis.[21 23] Such patients may have various types of histopathological abnormalities, including unselective atrophy of both type I and type II fibres, increased intracellular lipid droplets, scattered necrosis and moth-eaten fibres.[18] More specific abnormalities include selective loss of thick (myosin) myofilaments,[23 24] inexcitability of muscle membranes[25] and acute type II muscle fibre atrophy.[26]

Only a minority of our patients had increased serum CK concentrations. These increases were slight to moderate despite the fact that many patients had recent trauma, major surgery or soft tissue inflammation. None was admitted because of asthma. Eight of 12 patients with severely reduced CMAP amplitudes had normal CK concentrations, rendering necrotizing myopathy a less likely mechanism. Muscle biopsy performed in two patients in whom myopathy was suspected revealed neurogenic changes accompanied by only slight myopathy. Such unspecific myopathy is frequently present in patients with CIP.[5]

Severe cases of CIP should be distinguished from the acute motor axonal variant of Guillain–Barré syndrome, which is an immune-mediated disease most commonly associated with *Campylobacter jejuni* infections.[27] In contrast, CIP is a non-immune disorder restricted to ICU patients and related closely to severe infection or trauma of virtually any type, including sepsis and the systemic inflammatory response syndrome.[1,28] Unlike in Guillain–Barré syndrome, there is no evidence of inflammation in nerve biopsies.[1] Thus the pathogenesis of the two syndromes and the setting in which they occur is invariably different. To the best of our knowledge, no critically ill patient developing flaccid tetraplegia has yet been diagnosed with the axonal variant of Guillain–Barré syndrome. However, recognizing occasional patients in the ICU with Guillain–Barré syndrome is important because they may respond to plasma exchange and i.v. immunoglobulins.[28] Unfortunately, electrodiagnostic criteria allowing differentiation of motor axonal Guillain–Barré syndrome from CIP have not yet been established, making further investigations (e.g. lumbar puncture and nerve biopsy) necessary.

Other diagnostic considerations include damage to anterior horn cells resulting from acute or chronic spinal cord ischaemia[2,29,30] and acute motor neuropathy associated with administration of non-depolarizing neuromuscular blocking agents.[1] No episodes of severe hypoxia or hypotension occurred in our patients and anterior horn cell changes suggestive of ischaemia probably occurred only preterminally in two autopsy cases.[5] Neuromuscular blocking agents were administered in our patients only infrequently and on an intermittent basis. In none did repetitive nerve stimulations suggest disturbance of neuromuscular transmission. In addition, only the non-steroidal agent atracurium was used.

Until now, the pathophysiological events that cause CIP have remained unclear. Although a variety of potential causes such as types of primary illness or injury, medications (e.g. aminoglycosides and neuromuscular blocking agents) and specific nutritional deficiencies have been considered, retrospective and prospective studies failed to implicate them as causative factors.[1] Bolton has speculated that the mechanisms responsible for the systemic effects of sepsis may also cause axonal degeneration.[1] As a mechanism, he suggested disturbances in the microcirculation of peripheral nerves. However, biopsies from affected patients did not reveal fascicular infarction, microangiopathy, oedema or intravascular thrombus formation.[5,31] Moreover, this concept would not explain the predominance of CIP for motor nerve involvement.

In summary, CIP occurs frequently in septic patients and involves predominantly motor nerve fibres. Affected patients show an unusual combination of normal SNAP amplitudes, markedly decreased CMAP amplitudes and prominent denervation. Bedside electrophysiology may help to diagnose and monitor CIP, thus avoiding futile attempts to wean patients from the ventilator. Recognizing the predilection for motor nerves may be helpful in clarifying the pathogenesis of the disease.

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# Propofol attenuates formation of lipid peroxides in tourniquet-induced ischaemia–reperfusion injury

S. KAHRAMAN, K. KILINÇ, D. DAL AND K. ERDEM

## Summary

We studied 20 adult ASA I patients undergoing elective peripheral surgery allocated randomly to one of two groups. In the propofol group (*n*=9) anaesthesia was induced with propofol and fentanyl followed by continuous infusion of propofol. In the control group (*n*=11), after induction of anaesthesia with thiopentone and fentanyl, anaesthesia was maintained with isoflurane. Concentrations of lipid peroxides in both plasma and muscle tissue samples were measured as thiobarbituric acid-reacting substances (TBARS). Plasma TBARS concentrations increased significantly in the control group at 1, 5, 15, 30 and 45 min after release of the tourniquet to mean 1.83 (SD 0.13), 2.00 (0.12), 2.25 (0.14), 2.30 (0.12) and 2.41 (0.14) μmol litre$^{-1}$, respectively, compared with pre-reperfusion values (1.64 (0.14) μmol litre$^{-1}$). In the propofol group this was significant only at 30 min (1.85 (0.03) *vs* 1.74 (0.04) μmol litre$^{-1}$). TBARS concentrations of reperfused muscle tissue were significantly higher than pre-reperfusion concentrations in the control group (70.30 (10.06) *vs* 52.13 (5.73) nmol/g wet tissue). We conclude that propofol attenuated ischaemia–reperfusion-induced lipid peroxidation in the therapeutic doses used in anaesthesia. (*Br. J. Anaesth.* 1997; **78**: 279–281).

**Key words**
Anaesthetics i.v., propofol. Muscle skeletal, lipid peroxides. Complications, ischaemia–reperfusion injury.

Re-introduction of oxygen to an ischaemic or hypoxic tissue has been shown to cause additional insult to the tissue (reperfusion injury). Reactive oxygen species which damage cellular components and initiate the lipid peroxidation process are known to be responsible for the ischaemia–reperfusion injury. Lipid peroxidation is a chain reaction leading to oxidation of polyunsaturated fatty acids which, in turn, disrupts the structure of biological membranes and produces toxic metabolites such as malondialdehyde (MDA). The thiobarbituric acid assay, which measures MDA, has served as the most commonly used method for measuring lipid peroxidation.

Propofol (2,6-diisopropylphenol) is chemically similar to phenol-based free radical scavengers such as butylated hydroxytoluene and the endogenous antioxidant α-tocopherol (vitamin E).[1–3] Propofol has been shown to exhibit significant antioxidant activity *in vitro*, reacting with free radicals to form a phenoxyl radical.[3 4] Although Green, Bennett and Nelson[1] suggested that the antioxidant activity of propofol may not be clinically relevant, this effect has also been demonstrated at anaesthetic concentrations.[2] However, no clinical study has been conducted in humans to investigate the antioxidant effect of anaesthetic doses of propofol in ischaemia–reperfusion injury of skeletal muscle.

Therefore, we have determined if infusion of propofol would prevent the formation of lipid peroxides as a result of tourniquet-induced ischaemia–reperfusion injury in surgery of the limbs.

## Patients and methods

After obtaining Ethics Committee approval and informed patient consent, we studied 20 adult, ASA I patients undergoing peripheral surgery using a tourniquet. Patients were allocated randomly by closed envelope method to one of two groups: propofol (*n*=9) and isoflurane (control, *n*=11). No patient was receiving vitamin supplements. All patients were premedicated with diazepam 10 mg orally, 45 minutes before surgery. In the propofol group anaesthesia was induced with propofol 2–2.5 mg kg$^{-1}$ and fentanyl 3 μg kg$^{-1}$ followed by continuous infusion of propofol at a rate of 10 mg kg$^{-1}$ h$^{-1}$, reducing to 8 and 6 mg kg$^{-1}$ h$^{-1}$, respectively, at 10-min intervals. The maintenance dose was adjusted to clinical signs and anticipated demand. In the control group anaesthesia was induced with thiopentone 5 mg kg$^{-1}$ and fentanyl 3 μg kg$^{-1}$, and maintained with 1% isoflurane. Vecuronium 0.1 mg kg$^{-1}$ was given to facilitate tracheal intubation in both groups and the lungs were ventilated with 60% nitrogen in oxygen. The tourniquet was applied at a pressure approximately twice the systolic arterial pressure.

Using heparin-locked i.v. catheters, sequential

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venous blood samples were obtained from the antecubital vein of the contralateral arm. The dorsal vein of the foot was used for i.v. fluid and propofol infusions. During lower limb operations one arm was used for blood sampling and the other for i.v. fluid infusions.

Blood samples for lipid peroxidation analysis were obtained immediately before and 1, 5, 15, 30, 45 min after tourniquet release. Blood samples for measurement of blood urea nitrogen, creatinine, creatinine phosphokinase, lactate, sodium, potassium and calcium concentrations and muscle tissue biopsy samples were obtained immediately before (control) and 20 min after release of the tourniquet (reperfusion).

Plasma samples were centrifuged immediately. The supernatant and muscle tissue samples were stored at −70 °C until analysis. Concentrations of lipid peroxides in both muscle tissue and plasma samples were measured as thiobarbituric acid-reacting substances (TBARS). Frozen tissues were immediately weighed and homogenized in 10 volumes of ice-cold phosphate buffer (50 mmol litre$^{-1}$, pH 7.4) using a glass–glass homogenizer (B. Brown, Germany). The homogenate (0.5 ml) was mixed with 3 ml of 1% $H_3PO_4$. After addition of 1 ml of TBA reagent (0.67%) the tubes were heated in boiling water for 45 min. The colour formed was extracted into 4 ml of n-butanol. After centrifugation, the colour intensity of the butanol layer was measured at 532 nm using a Shimadzu UV-120-02 model spectrophotometer.[5] Tetramethoxypropane was used as the standard and concentrations of TBARS were calculated as nanomoles of malondialdehyde (MDA) per gram of wet tissue. Lipid peroxide concentrations in plasma were measured as described by Wade and van Rij.[6] Concentrations of TBARS in serum were calculated as micromoles per litre.

Significant differences between groups were analysed using the Mann–Whitney *U* test. Intragroup comparisons were performed by Wilcoxon matched pairs test and $P<0.05$ was considered statistically significant.

## Results

There were no significant differences between groups in age, weight, sex distribution or tourniquet time (table 1). Plasma concentrations of TBARS increased significantly in the control group at 1, 5, 15, 30 and 45 min after release of the tourniquet by mean 1.83 (SD 0.13), 2.00 (0.12), 2.25 (0.14), 2.30 (0.12) and 2.41 (0.14) μmol litre$^{-1}$, respectively, compared with pre-reperfusion values (1.64 (0.14) μmol litre$^{-1}$) (fig. 1). In contrast, there were only slight increases at 15, 30 and 45 min in the propofol group, and this was significant only at 30 min (1.80 (0.03), 1.85 (0.03) and 1.83 (0.06) μmol litre$^{-1}$, respectively, *vs* 1.74 (0.04) μmol litre$^{-1}$).

*Table 1* Patient characteristics (mean (SD or range) or number)

| | Group I (isoflurane) | Group II (propofol) |
|---|---|---|
| *n* | 11 | 9 |
| Age (yr) | 36.55 (29–59) | 36.77 (18–58) |
| Weight (kg) | 73.34 (15.5) | 80.55 (13.7) |
| Sex (M/F) | 7/4 | 6/3 |
| Operation (*n*) | | |
| Median nerve exploration | 3 | 3 |
| Ulnar nerve exploration | 1 | — |
| Intramuscular haemangioma | 2 | 1 |
| Intramuscular hamartoma | 1 | 1 |
| Achilloplasty | 2 | 1 |
| Contracture release | 2 | 3 |
| Tourniquet time (min) | 82.55 (26.1) | 89.20 (23.7) |
| Anaesthesia time after tourniquet release (min) | 46.36 (14.5) | 47.78 (12.5) |

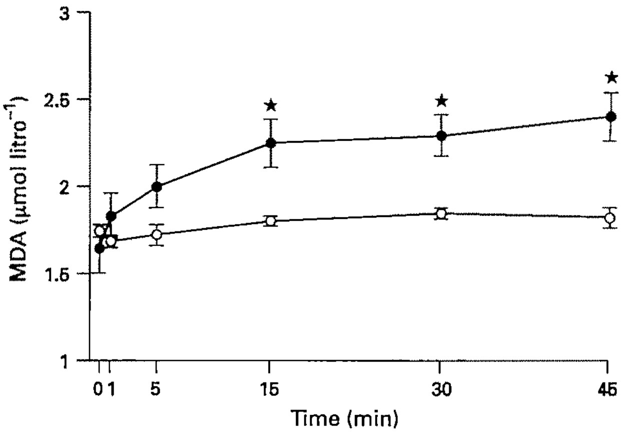

*Figure 1* Plasma MDA concentrations before (0) and 1, 5, 15, 30 and 45 min after release of the tourniquet in the isoflurane (●) and propofol (○) groups. *$P<0.05$ between groups.

TBARS concentrations in muscle tissue after 20 min of reperfusion were significantly higher than pre-reperfusion concentrations in the control group (70.30 (10.06) *vs* 52.13 (5.73) nmol/g wet tissue) while there were no significant differences in the propofol group (38.13 (5.26) *vs* 40.16 (5.68) nmol/g wet tissue). TBARS concentrations in reperfused muscle tissue were significantly different between groups ($P=0.0069$).

In two patients (22%) in the propofol group and four patients in the control group the anaesthetic was discontinued before 45 min of reperfusion. Plasma electrolyte, creatinine, blood urea nitrogen, lactate and creatinine phosphokinase concentrations were not significantly different after reperfusion in either group and differences between groups were not significant.

## Discussion

Although skeletal muscle is fairly resistant to ischaemic injury, ischaemia–reperfusion injury has been documented in previous studies. Concannon and colleagues[7] showed a significant increase in MDA production within 2 h in a rabbit model of tourniquet-induced skeletal muscle ischaemia–reperfusion injury. The results of our study (35% increase in MDA concentrations in muscle tissue after 20 min of reperfusion and 47% increase in systemic blood within 45 min after reperfusion) were comparable with the results of Concannon and colleagues.

Studies using isolated organelles have shown that propofol inhibits lipid peroxidation induced by oxidative stress in rat liver mitochondria, microsomes and brain synaptosomes.[2,4] However, its effects on skeletal muscle ischaemia–reperfusion injury have not been examined. Intentional ischaemia (tourniquet)–reperfusion for bloodless upper limb surgery has been accepted as a good human model for ischaemia–reperfusion injury. In this human model of ischaemia–reperfusion injury, we examined the effect of the i.v. anaesthetic propofol on lipid peroxide formation. As it was shown that maintenance of general anaesthesia with clinical relevant concentrations of nitrous oxide or isoflurane were not associated with an increase in toxic oxygen metabolites[8] we preferred to use isoflurane in the control group. While there was a significant increase in MDA concentrations in both plasma and muscle tissue in the isoflurane group, there was only a slight increase in plasma concentrations in the propofol group. The absence of a significant difference in biochemical variables at 20 min of reperfusion suggests that our measurements were probably performed after the initial rapid washout of accumulated tissue lactate and other substances.

We conclude that propofol attenuated ischaemia–reperfusion-induced lipid peroxidation when given in the therapeutic doses used in anaesthesia; this suggests that its oxygen free radical scavenging activity during anaesthesia is likely to be clinically significant.

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# Auditory evoked response, median frequency and 95% spectral edge during anaesthesia with desflurane and nitrous oxide

R. M. SHARPE, D. NATHWANI, S. K. PAL, M. D. BRUNNER, C. THORNTON, C. J. DORÉ AND D. E. F. NEWTON

## Summary

We have studied in 12 patients the effect of desflurane in nitrous oxide on the electroencephalogram (EEG) and the early cortical auditory evoked response (AER). After induction with desflurane, patients' lungs were ventilated to maintain three different end-expiratory concentrations of desflurane (1.5, 3 and 6%) during four consecutive 10-min periods before surgery. As the end-expiratory concentration of desflurane was increased, Pa and Nb (AER) amplitudes decreased and their latencies increased, and spontaneous EEG showed an increase in amplitude and a slowing of frequency. A linear relationship was demonstrated between $\log_{10}$ concentration of desflurane and all variables ($P=0.001$). Pa amplitude showed the greatest linearity followed by the derived variable F95 of the EEG. From regression slopes, mean percentage changes of each variable were calculated for a 1 MAC change in desflurane concentration. Pa amplitude showed the largest change (mean 49% (95% confidence interval 40–56%) decrease for a 1 MAC increase). This was greater than that of F95 for a similar confidence interval, indicating better resolution. This study confirms that the early cortical AER is affected by desflurane in a similar manner to that of other anaesthetic agents and as such remains the most promising EEG derived measure of depth of anaesthesia. (*Br. J. Anaesth.* 1997; **78**: 282–285).

**Key words**
Anaesthesia, depth. Anaesthetics volatile, desflurane. Monitoring, electroencephalography. Brain, evoked potentials.

Previous studies have shown that increasing concentrations of inhalation[1 2] and i.v.[3 4] anaesthetic agents produce graded reductions in amplitude and prolongation of the latency of waves Pa and Nb of the early cortical auditory evoked response (AER). These changes are not agent specific and are antagonized by surgical stimulation,[5] suggesting that the AER may be a useful measure of anaesthetic depth.

The electroencephalograph (EEG) has been shown to slow with increasing concentration of anaesthetic, although enflurane has an opposite effect.[6] EEG data may be analysed to provide quantitative indices. Variables can be derived from the power spectra of the EEG, for example median frequency or F50, which is the frequency below which 50% of the signal power is present, [7] and spectral edge frequency or F95 which is the frequency below which 95% of the signal power is present.[8] Spectral edge and median frequencies have been shown to decrease with increasing concentrations of thiopentone,[9] etomidate,[10] isoflurane[11] and desflurane.[12]

The EEG and AER effects of new agents have to be characterized if they are to remain useful tools for monitoring depth of anaesthesia. The aims of this study were to investigate the effects of desflurane on the early cortical AER and to compare these with changes in median frequency and spectral edge of the EEG.

## Patients and methods

We studied 12 patients, aged 31–65 yr, undergoing elective surgery requiring tracheal intubation. All gave informed consent to participate in the study, the design of which was approved by the Harrow District Ethics Committee.

After premedication with morphine 10 mg and atropine 0.4 mg i.m., anaesthesia was induced by inhalation of desflurane and 66% nitrous oxide (end-tidal) in oxygen. When anaesthesia was achieved, vecuronium 0.1 mg $kg^{-1}$ was given and the patient's trachea intubated. The lungs were ventilated with desflurane and 66% nitrous oxide in oxygen, a concentration selected according to a predefined sequence to which patients had been allocated randomly. Patients received either 1.5, 3 or 6% desflurane (end-expiratory concentrations) for 10 min and then the concentration was changed. All patients received each of the three possible concentrations. During a fourth period, the concentration of the preceding period was repeated. This study

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*Table 1* Change in variables for a 1 MAC change in desflurane, calculated from the regression equation for each variable All Wald statistics were significant ($P<0.001$)

| Variable | Direction of change | Mean % change | 95% CI for change | Wald statistic |
|---|---|---|---|---|
| Pa latency | Increase | 9.9 | 4 5–15.5 | 13 0 |
| Nb latency | Increase | 8.0 | 3.1–13 1 | 10.1 |
| Pa amplitude | Decrease | 49 | 40–56 | 75.3 |
| Nb amplitude | Decrease | 43 | 32–52 | 43.6 |
| F50 | Decrease | 25 | 11–37 | 14.6 |
| F95 | Decrease | 33 | 25–41 | 65.3 |

*Table 2* Geometric mean (95% confidence intervals) for Pa and Nb amplitude and F50 and F95 to illustrate the effect of period

| Period | Pa amplitude | Nb amplitude | F50 | F95 |
|---|---|---|---|---|
| 1 | 0 21 | 0.20 | 2.82 | 10 88 |
|  | 0.17–0.26 | 0.15–0.26 | 2.20–3.61 | 9 81–12.07 |
| 2 | 0.21 | 0.18 | 2.06 | 8.78 |
|  | 0.18–0.26 | 0 14–0.23 | 1.61–2.64 | 7.92–9 75 |
| 3 | 0.15 | 0.12 | 1.65 | 7.96 |
|  | 0.12–0.18 | 0.09–0.16 | 1.29–2.11 | 7 17–8.83 |
| 4 | 0.16 | 0.13 | 1.62 | 8.70 |
|  | 0.13–0.19 | 0.10–0.17 | 1 27–2 08 | 7.85–9.66 |
| Probability | 0.009 | 0 01 | 0 003 | <0 001 |

design ensured that each concentration of desflurane followed every other concentration, including itself, an equal number of times so that overall, any "carry over" effect of one period to the next would be cancelled. It also allowed interactions between dose and time to be studied. Fresh gas flow was adjusted to maintain end-expiratory carbon dioxide partial pressure at 4.5–5 kPa. Neuromuscular block was maintained at a level of two responses on the train-of-four by infusion of vecuronium. End-expiratory concentrations of nitrous oxide, carbon dioxide and desflurane were measured using a calibrated Datex Ultima gas analyser.

The EEG and AER recorded from adhesive silver–silver chloride electrodes attached to the mastoid and forehead were stored and analysed on a PC-based system described previously.[13] The auditory stimulus was a rarefaction click at 6 per second delivered to both ears via close fitting ear pieces, 75 dB above the average hearing threshold. The EEG signal was analogue filtered on input with bandwidths of 25–500 Hz to produce the AER recording. Although the EEG and AER were recorded continuously throughout the study, only the last 2 min 40 s (1024 sweeps of AER) of each period, when equilibration was considered to have occurred, were used to derive the data. From the printed AER waveforms, Pa and Nb amplitudes and latencies were measured by an observer blind to the dose of desflurane.

For statistical analysis, all AER variables were normalized by $\log_{10}$ transformation. To test for a significant effect of dose and period on the AER and EEG variables, we used analysis of variance (ANOVA) with the restricted maximum likelihood (REML) procedure in Gentstat.[14] The Wald statistic (REML) which follows an approximate chi-square distribution with 1 degree of freedom tested for linearity with log dose.

## Results

Of the 12 patients studied, eight were females undergoing major gynaecological surgery and four were males undergoing major orthopaedic surgery. Mean age was 46 (range 31–62) yr and mean weight 77 (SD 10) kg.

As the end-expiratory concentration of desflurane was increased, Pa and Nb amplitudes decreased and their latencies increased, and the EEG showed an increase in amplitude and a slowing of frequency. An example from one patient is shown in figure 1.

A linear relationship was demonstrated between $\log_{10}$ dose and all variables over the concentration range studied. For example, mean Pa amplitude and F95, plotted against end-expiratory desflurane concentration ($\log_{10}$ scale) are shown in fig. 2.

For all variables the Wald statistic was highly significant at $P<0.001$ (table 1). The Wald statistic

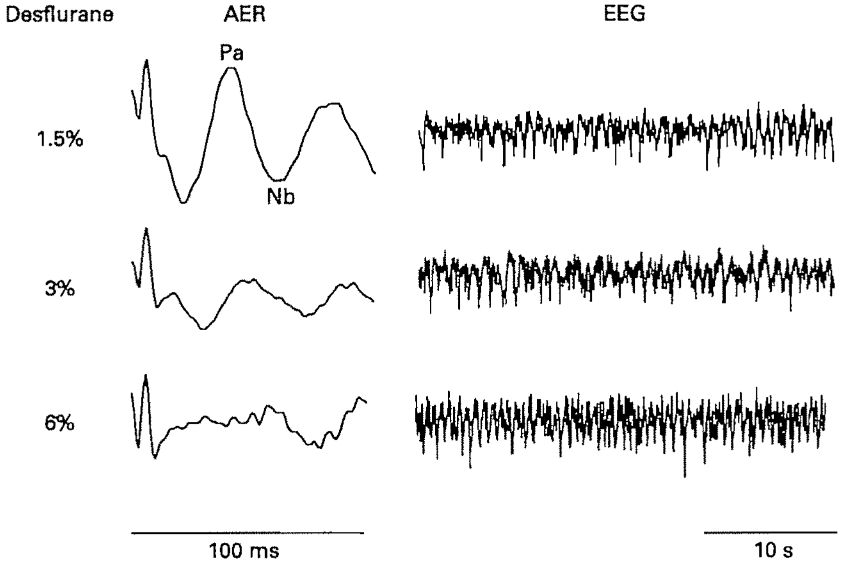

*Figure 1* An example from one subject, showing the effect of increasing end-expiratory desflurane on the AER and EEG. In the AER the amplitudes of Pa and Nb decreased and their latencies increased. The EEG shows an increase in amplitude and slowing of frequency.

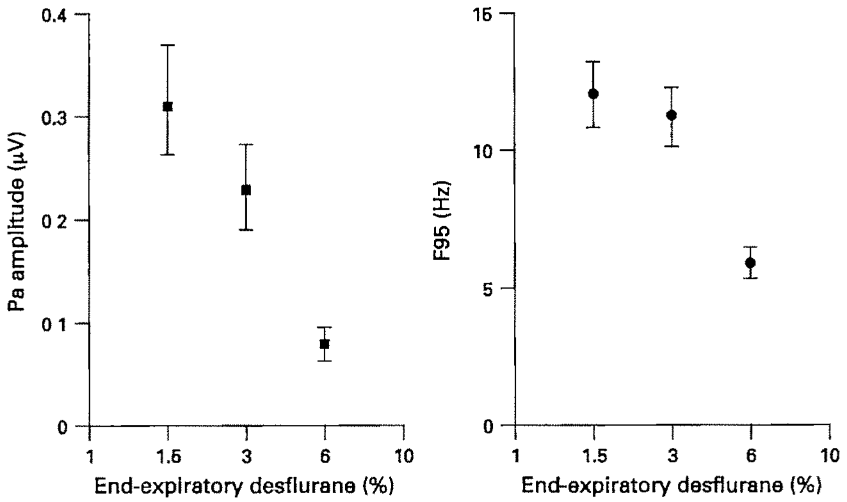

*Figure 2* Mean (95% confidence intervals) Pa amplitude and F95, plotted against desflurane concentration (log scale).

tests for linearity and the larger the number the more linear the relationship. Pa amplitude had the highest value, followed by F95. Regression slopes (with SEM) for each variable with $\log_{10}$ dose were calculated. From these, the percentage change and 95% confidence intervals were calculated for a 1 MAC increase in desflurane concentration. For example, a 1 MAC increase in desflurane concentration produced a 49% (95% confidence interval 40–56%) decrease in Pa amplitude, and a 33% (25–41%) decrease in spectral edge. Percentages are appropriate rather than the original units because the AER and EEG variables were $\log_{10}$ transformed for data analysis.

A period effect was seen for Pa and Nb amplitudes, and F50 and F95 ($P$=0.009, 0.01, 0.003 and <0.001, respectively). The means of these variables were significantly lower in the later periods of administration (table 2). In the case of Pa amplitude and F95, a significant interaction between dose and period was seen ($P$=0.05 and <0.001, respectively). For the low desflurane concentration these variables decreased in the later periods. At medium and high concentrations no clear trend emerged.

## Discussion

Desflurane reduced the amplitudes of waves Pa and Nb of the AER and increased their latencies. Median frequency (F50) and spectral edge (F95) were reduced by desflurane. In all cases these effects were linearly dose related.

The significant effect of period on the variables Pa and Nb amplitude and F50 and F95 suggests that although end-expiratory desflurane concentration equilibrated rapidly with inspired desflurane concentration in each of the four periods, equilibration in the brain had not occurred in the earlier periods. In the later periods the means of the above variables were lower (the patients were deeper) despite being exposed to the same concentrations of desflurane (table 2).

In addition, an interaction between dose and period was seen for Pa amplitude and F95. For the lowest desflurane concentration, these variables were lower (the patients were deeper) in the later periods. No trend was seen for the medium and high concentrations. As the low desflurane concentration could only follow a higher concentration (except in the first period) this effect could be attributed to a carry over effect from the preceding period. If this were true one would expect to see the converse effect in the high desflurane concentration group. However, such an effect was not observed. There are two possible explanations for this: first, the same equilibration effects cannot be assumed during wash-in and wash-out; second, for the AER variables, the effect may have been too subtle to detect at the higher desflurane concentrations where the average curves were much flatter.

Changes in the early cortical AER were similar to those of other anaesthetics we have studied previously.[1–4] Halothane, enflurane, isoflurane, etomidate and propofol reduced amplitude and increased the latency of the Pa and Nb waves of the AER in a dose-related manner. Confirmation that new anaesthetic agents produce similar changes in the AER strengthens its value as a method of monitoring depth of anaesthesia.

Changes in the AER were more marked when the concentration of desflurane decreased from 3% to 1.5% compared with changes in EEG variables (see fig. 1). Thus the AER may be a more sensitive indicator of anaesthetic depth at low desflurane doses than the EEG.

Pa amplitude showed the best linear relationship with desflurane concentration (largest Wald statistic, F95 was the next largest (table 1)). Also, Pa amplitude showed a larger percentage change for 1 MAC desflurane compared with F95 for the same confidence intervals, suggesting greater resolution of measurement.

Rampil and colleagues investigated the quantitative effects of desflurane on the EEG[12] and found a progressive decrease in these variables with increasing concentration. However, at comparable desflurane concentrations, F50 and F95 were higher in their study compared with ours. Patients in our study were deeper for equivalent desflurane concentrations, possibly because of premedication with morphine and atropine as an adjunct to induction with desflurane. We used this premedication and nitrous oxide for comparison with data from our previous studies with other volatile agents.[1 2] In addition, the higher mean age of the patients in the this study of 45.8 yr compared with 23.8 in the study of Rampil and colleagues would contribute to this difference. Burst suppression was not seen in our study.

In summary, we observed that desflurane had similar actions on the early cortical AER as other anaesthetic agents studied previously and it compared well with EEG spectral analysis variables. Pa amplitude (AER) showed better linearity and resolution than the best of the EEG variables (F95). The results also suggested that the AER may be a more sensitive indicator of anaesthetic depth at low desflurane doses and the EEG more sensitive at higher desflurane concentrations. As such, the early cortical AER remains the most promising EEG derived measure of depth of anaesthesia.

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# Effect of percutaneous local anaesthetics on pain reduction during pulse dye laser treatment of portwine stains

D. F. McCAFFERTY, A. D. WOOLFSON, J. HANDLEY AND G. ALLEN

## Summary

We have used EMLA, 4% amethocaine gel and placebo for facial portwine stains, for a period of 1 h, in a double-blind study. After removal of the preparations from the skin surface, each area was treated with six pulses of the laser, each 5 mm in diameter. Any pain noted immediately after treatment was recorded using both visual analogue (VAS) and verbal rating (VRS) scores. Twenty nine patients completed the study and statistical analysis of the results indicated that both EMLA and 4% amethocaine gel were superior to placebo ($P<0.001$). However, when EMLA and 4% amethocaine gel were compared, the amethocaine preparation was significantly better ($P<0.05$, VAS; $P<0.005$ VRS) than EMLA in reducing pain caused by the laser treatment. (*Br. J. Anaesth.* 1997; **78**: 286–289).

**Key words**
Anaesthetics local, amethocaine. Anaesthetics local, EMLA. Complications, portwine stains.

Portwine stains (PWS) are benign, disfiguring vascular birthmarks consisting of ectatic dermal capillaries. They are relatively common with an incidence of approximately 0.3% in the general population. The former are caused by malformed blood vessels close to the skin surface. As approximately 80% of portwine stains are found on the face or neck this disfiguration can lead to various psychosocial problems. Current treatment of these lesions involves the use of a pulse dye laser which emits a pulsed coherent light of wavelength 585 nm which is absorbed selectively by oxyhaemoglobin in capillaries. The pulse duration of 450 μs is less than the thermal relaxation time of the dermal capillaries which enables the incident laser light to photocoagulate the capillaries while minimizing thermal diffusion into surrounding tissue. As a result, the possibility of scarring is reduced. The pulse dye laser has proved to be both effective and safe and is currently considered the treatment of choice for portwine stain birthmarks.

However, this treatment can be painful, especially if large areas are involved. Young children often require general anaesthesia before this procedure and older patients some type of local anaesthesia. It has been reported that EMLA cream, when applied for a period of 1–2 h before treatment, can reduce the pain associated with this procedure.[1] In our experience, however, when applied for 2 h or more before treatment, EMLA provided only partial pain relief.

An amethocaine-based preparation has been shown to provide more effective percutaneous local anaesthesia than EMLA.[2] Therefore, the purpose of this double-blind study was to compare the efficacy of the two formulations with placebo for prevention of pain during treatment of portwine stains by pulse dye laser.

## Patients and methods

### FORMULATIONS

EMLA was obtained from Astra, UK, and amethocaine gel 4% w/w was prepared as described previously.[2] A placebo gel was also prepared to match the two active formulations. All three formulation were packaged into standard lacquered aluminium tubes, using standard pharmaceutical methods. Each tube was then assigned a randomized number.

### PATIENT SELECTION

Ethics Committee approval was obtained for the study and of the 30 patients enrolled, 29 completed the treatment. Inclusion criteria were age more than 12 yr of age, a portwine stain of at least 3×3 cm and no adverse response after 12 weeks to a test treatment with the pulse dye laser at a fluence of 6.25–6.5 J cm$^{-2}$.

### STUDY DESIGN

The design of the study was organized so that each patient could act as their own control. In order to facilitate this, hollow adhesive templates (0.1 cm thick) were made with internal dimensions of 3×1 cm. Three of these were then attached to the

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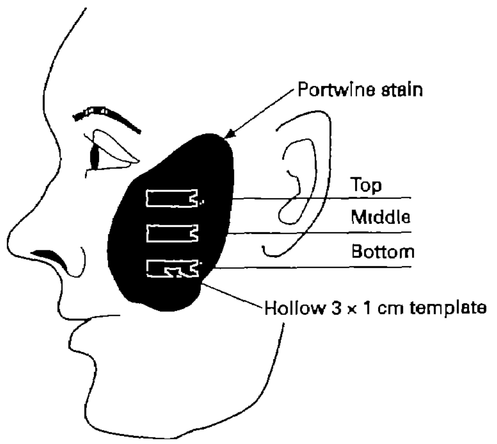

*Figure 1* Positioning of templates for facial portwine stain.

portwine stain area as shown in figure 1. Thereafter, 1 g of each formulation was applied, in a random manner, to the interior of each template. All three templates were then covered with an occlusive dressing and left for 1 h. At the end of this period all three formulations were removed from the portwine stain and the area wiped clean. Six pulses of the laser were then given within each treated area and the pain response noted immediately by the patient using visual analogue (VAS) and verbal rating (VRS) scores.

### PAIN ASSESSMENT

We used both VAS and VRS scores for assessment of pain. With the former, patients were asked to mark a point on a 10-cm horizontal line that corresponded to the degree of pain they felt immediately after each treatment. One end of the line represented no pain while the other was designated as very painful. Four categories of VRS pain scoring were used; 1=no pain, that is complete anaesthesia; 2=very slight pain (almost complete anaesthesia); 3=moderate pain (some anaesthesia has occurred); 4=very painful (no apparent anaesthesia). For statistical purposes scores 1 and 2 were considered clinically acceptable whereas a score of 3 or 4 implied that the treatment had been unsuccessful. VAS data were analysed by ANOVA and detailed comparisons were undertaken by the Scheffé test. In contrast, VRS results were analysed using the chi-square method in the form of a 2×3 contingency table.

### LASER TREATMENT

All patients were treated using a Photogenica V pulse dye laser (Cynosure). Test treatments consisting of a few pulses with the 5 mm spot at fluences of 6.25–6.5 J $cm^{-2}$ were undertaken and the patient reviewed at 12 weeks. If no adverse effects had occurred after this period then the patient received 6 pulses at a consistent fluence of 6.25–6.5 J $cm^{-2}$ applied to the centre of each template.

## Results

VAS data from the 29 patients are shown in figure 2. Details of the VRS results, showing the distribution of all pain scores, are illustrated in figure 3. In contrast, grouping of pain scores 1 and 2, and 3 and 4 are shown in figure 4. Statistical analysis of the data represented by figure 2, using ANOVA, indicated that there was a significant difference between the formulations ($P<0.001$). More detailed analysis, using the Scheffé multi-comparison method, indicated that both amethocaine and EMLA were

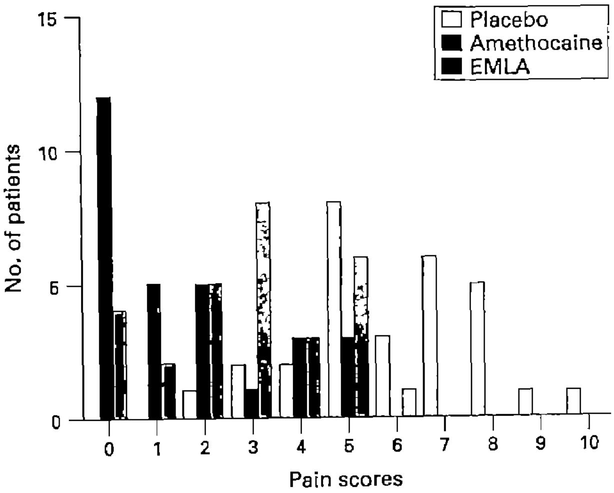

*Figure 2* VAS pain scores for the 29 patients in the three groups.

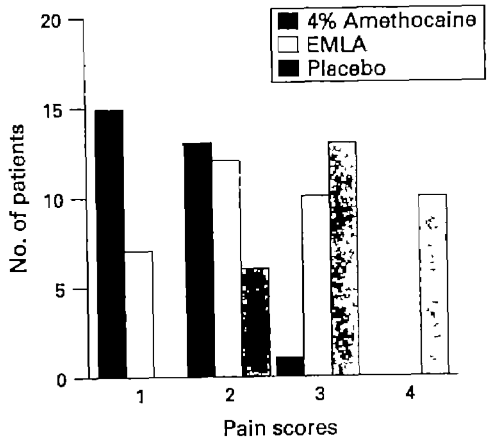

*Figure 3* Number of patients in each VRS pain score group.

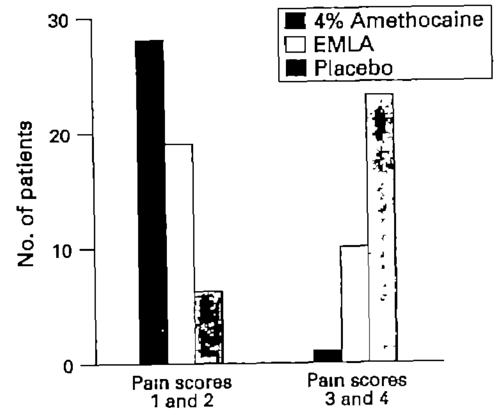

*Figure 4* Number of patients with clinically acceptable percutaneous local anaesthesia (VRS 1 and 2) and clinically unacceptable anaesthesia (VRS 3 and 4).

*Table 1* 2×3 contingency table for chi-square analyses of VRS data

| | 4% Amethocaine | EMLA | Placebo | Total |
|---|---|---|---|---|
| Clinically acceptable anaesthesia | 28 | 19 | 6 | 53 |
| Clinically unacceptable anaesthesia | 1 | 10 | 23 | 34 |
| Total | 29 | 29 | 29 | 87 |

significantly better than placebo in producing percutaneous local anaesthesia ($P<0.001$). This test also demonstrated that the amethocaine-based formulation was more effective than EMLA in reducing pain ($P<0.05$).

The results illustrated in figure 4 are presented in the form of a 2×3 contingency table (table 1). Statistical analyses of these data using the chi-square method indicated that the formulations tested were not equivalent ($P<0.001$). More detailed examination showed that both active preparations were better than placebo ($P<0.001$) and that 4% amethocaine was significantly better than EMLA ($P<0.005$).

## Discussion

The purpose of the present study was to evaluate pain reduction associated with the use of the pulse dye laser when treating portwine stains. However, pain is a subjective phenomenon and although sensory thresholds for pain vary little between individuals, the tolerance level varies considerably between cultures, individuals and even in the same person at different times.[3] This occurs because the subjective intensity of pain depends not only on the extent of the stimulus but also on the degree to which it occupies the subject. Redirection of attention can weaken the sensation and, in extreme conditions such as the stress of an accident or hypnosis, can abolish it .[4] Because of the difficulties in assessing pain, we used two different types of pain measurement—VAS and VRS. The results shown in figure 2 demonstrated typically the variety of responses obtained from VAS assessment. However, it can be seen that the highest individual score for either of the active preparations was 6 while almost 50% of the placebo responses exceeded this. One patient had a maximum painful score (10) for placebo. At the other end of the scale we observed that the amethocaine-based formulation gave more 0 scores than EMLA. It is clear from the statistical analyses of the data that not only were both active preparations better than placebo but that the amethocaine-based formulation was superior to EMLA.

Analyses of the verbal descriptor score showed a similar trend. A particular advantage in using this technique was that it allowed distinction between clinically acceptable (pain scores 1 and 2) or unacceptable (pain scores 3 and 4) topical anaesthesia. Amethocaine accounted for most patients in the pain score 1 category (15) (fig. 3); less than 25% of EMLA-treated patients were in this category. Approximately the same number of patients had a pain score of 2 when either amethocaine or EMLA was used. However, although only one individual had a pain score of 3 for the amethocaine formulation, 10 EMLA-treated patients had this score. No individual scored 4 for either active preparation. Although none of the placebo-treated patients had a pain score of 1, six scored 2 (i.e. clinically acceptable anaesthesia) and approximately 33% scored 3. These results indicated a placebo response but both active formulations were significantly better than placebo. Previous experience has shown that there is almost no placebo response when trained volunteers are used, that is individuals are pretreated with the active formulations so that they can assess the sensation of percutaneous local anaesthesia before taking part in the formal clinical study.[2 5] Although both the VAS and VRS methods gave the same results (after statistical analyses) the VRS data were more highly significant. In a previous study, Ashinoff and Geronemus[1] examined the effects of EMLA on the efficacy of pulse dye laser treatment of portwine stains. The application time for EMLA was the same as in this study and although they claimed that adequate anaesthesia was attained, no quantitative data were reported to substantiate these claims. However, they concluded that the use of this formulation did not appear to adversely influence the efficacy of the pulse dye treatment.

It has been reported previously that 4% amethocaine was more effective than EMLA in reducing the pain of venepuncture.[2 5] This was, perhaps, not surprising considering the *in vitro* penetration characteristics of both preparations. It has been reported that approximately the same amount of amethocaine penetrated human skin from a 4% amethocaine formulation as did prilocaine and lignocaine from EMLA.[6] If this occurred *in vivo* then it would be expected that the amethocaine-based formulation would be more effective as the drug is approximately four times more potent than either prilocaine or lignocaine.[7]

The results of this study indicated clearly that even using the recommended application period of 1 h for EMLA did not appear to be sufficiently long to provide clinically acceptable percutaneous topical local anaesthesia in approximately 33% of patients (fig. 4). In contrast, 4% amethocaine provided satisfactory anaesthesia in all but one patient. A logical progression of the research would be to examine the effects of shorter application times for the amethocaine formulation as it has been demonstrated previously that a 30–40-min contact period was suitable for venepuncture.[2]

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LABORATORY INVESTIGATIONS

# Anaesthetic potency of inhalation agents is independent of membrane microviscosity

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## Summary

The decrease in membrane microviscosity of erythrocyte ghosts in the presence of clinically relevant concentrations of seven inhalation anaesthetic agents was studied using fluorescence polarization anisotropy of the membrane incorporated fluorescent probes 1,6-diphenyl-1,3,5-hexatriene and 1-[4-trimethylammoniumphenyl]-6-phenyl-1,3,5-hexatriene. All anaesthetic agents produced a dose-dependent decrease in anisotropy of both probes, indicating decreased membrane microviscosity. The reduction in anisotropy measured at the minimum alveolar concentration ($ED_{50}$) for anaesthesia was related inversely to the anaesthetic potency of the agent and was directly proportional to the hypothetical concentration of agent in the membrane calculated from lipid–water partition coefficients. These findings do not support the hypothesis that volatile anaesthetic agents act by increasing membrane microviscosity of the bulk lipid bilayer to produce anaesthesia. (*Br. J. Anaesth.* 1997; **78**: 290–295).

**Key words**
Measurement techniques, anisotropy. Potency, anaesthetic, MAC. Anaesthetics volatile. Theories of anaesthetic action, molecular.

The mechanism of action of inhalation anaesthetics remains unknown even though these agents are used widely in clinical practice. The anaesthetic potency of the volatile agents is correlated most closely with their solubility in non-polar solvents and lipid.[1–5] It has been implied from this relationship that volatile anaesthetic agents may act to alter neuronal membrane function.[3–5] This could occur either through a generalized perturbation of neuronal membrane bilayer structure, by non-specific interaction of membrane dissolved agents with bilayer lipids or by direct modification of neuronal membrane protein activity by interaction with specific hydrophobic binding sites on sensitive proteins. A variety of changes in membrane dynamic properties in the presence of volatile agents have been demonstrated by various biophysical techniques and include increased rotational motion, decreased phase transition temperature, decreased surface viscosity, weakened binding of interfacial water, volume expansion and competition of membrane hydrogen bonds (reviewed by Aloia, Curtain and Gordon[6]). Many of these phenomena have been observed at supra-clinical anaesthetic concentrations and it remains to be determined if any of these perturbations in membrane dynamic properties are relevant to the process of anaesthesia.

The activity and kinetics of membrane-bound enzymes and carrier proteins can be markedly affected by the fluidity of the lipid phase of the membrane.[7] Several neuronal protein activities have been reported to be sensitive to the presence of volatile agents[8–13] and some of these could be involved in the mechanism of anaesthesia. Modification of membrane dynamic properties by volatile anaesthetic agents may be sufficient to transduce the anaesthetic effect of agents in the nervous system. For example, a link between membrane lipid order and sodium channel activity has been proposed from a strong linear relationship between voltage-dependent uptake of $^{24}Na^+$ into isolated mouse brain synaptosomes and the decrease in fluorescence polarization of membrane incorporated probes, 1,6-diphenyl-1,3,5-hexatriene (DPH) and 1-[4-trimethylammoniumphenyl]-6-phenyl-1,3,5-hexatriene (TMA-DPH).[14] By analogy, it has been suggested that changes in protein function induced by membrane dynamic changes, such as the sodium channel, perhaps in conjunction with alterations in other synaptic processes, could result in modified membrane conductance or synaptic transmission and transduce the anaesthetic effect of membrane dissolved agents.[3–5]

If the primary action of the inhalation anaesthetics involves alteration of a property of the lipid bilayer to transduce the effect of agent in the membrane at a functional level, it would be predicted that when tested at equipotent concentrations for anaesthesia the volatile agents may be expected to produce the

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same degree of perturbation in that variable. Although not all biological membranes would be involved in transducing the anaesthetic effect, anaesthetic perturbation of membrane dynamics would be expected to be universal. To test this hypothesis, anaesthetic-induced increases in erythrocyte membrane microviscosity produced by clinically relevant concentrations of seven volatile anaesthetic agents were investigated to allow the degree of membrane perturbation at the $ED_{50}$ for anaesthesia for the agents to be determined. Probes studied were DPH, which incorporates into the core hydrophobic region of the lipid bilayer, and TMA-DPH, which localizes in the outer regions of the lipid bilayer by virtue of the cationic trimethylammonium group.[15] These probes intercalate between membrane lipid molecules and the fluorescence polarization anisotropy reports on the restriction of movement of the probe molecule and thus reflects largely the rotational movement of the probe in the membrane. The greater the polarization of the fluorescent emission in response to a polarized excitation the more restricted is the probe in the membrane. Thus fluorescent polarization anisotropy reports on the membrane microviscosity in the environs of the probe.

## Materials and methods

DPH and TMA-DPH were obtained from Molecular Probes Inc. (Eugene, Oregon, USA). Anaesthetic agents were obtained as follows: desflurane was a gift of Pharmacia (St Albans, Hertfordshire, UK), halothane and trichloroethylene were from ICI Pharmaceuticals (Macclesfield, Cheshire, UK), isoflurane and enflurane were from Abbott Laboratories Ltd (Maidenhead, Berkshire, UK), methoxyflurane was from C-Vet (Bury St Edmunds, Suffolk, UK) and nitrous oxide from BOC Ltd (Derby, Derbyshire, UK). Air and oxygen were from BOC Ltd. All other reagents used were of the highest grade available.

### ERYTHROCYTE GHOST MEMBRANES

Venous blood samples were collected from 10 healthy volunteers into tubes containing ethylenediaminetetraacetic acid as anticoagulant. Plasma and the buffy coat were removed after centrifugation at 1900 x g for 10 min at 4°C. Erythrocyte ghost membranes were prepared as reported previously[16] and stored at −20 °C until use.

### MEMBRANE MICROVISCOSITY MEASUREMENTS

Erythrocyte ghost membranes, 100 μg of protein $ml^{-1}$ in 1 ml of Tris-HCl 10 mmol $litre^{-1}$ (pH 7.4), were incubated in a thermistor-controlled water bath at 37±0.1 °C and volatile anaesthetic agents delivered at the required concentration from laser refractometer calibrated vaporizers (Ohmeda TEC (0–2% trichloroethylene; 1–3% methoxyflurane; 0–5% halothane; 0–4% isoflurane; 0–4% enflurane) or TEC 6 (0–20% desflurane)) via a manifold of 10 outlets, each delivering humidified air 60 ml $min^{-1}$ to each sample. The deadspace over each sample was 11 ml. Carrier gas flow through the vaporizers was 2 litre $min^{-1}$ and any excess gas not delivered to experimental tubes was exhausted to the atmosphere. The time taken for each agent to reach stable equilibrium in the aqueous phase was determined in preliminary experiments by following the decrease in DPH and TMA anisotropy with gas delivery at the lowest concentration of each agent to be studied until steady state anisotropy was attained (not shown). Equilibration times were confirmed at approximate MAC concentrations of agent delivered by gas chromatographic analysis using a Perkin-Elmer 8410 gas chromatograph[17] (table 1). Volatile agents (0.2% trichloroethylene, 0.5% methoxyflurane, 0.75% halothane, 1.25% isoflurane and 1.7% enflurane) were delivered for various times (0–60 min) to samples containing 100 μg of erythrocyte ghost membrane protein in 1 ml of Tris-HCl 10 mmol $litre^{-1}$ (pH 7.4). Aliquots (100 μl) were mixed with n-heptane 100 μl (halothane, isoflurane, enflurane) or toluene 100 μl (trichloroethylene, methoxyflurane) in glass vials on ice. The vials were sealed to prevent evaporation before analysis. The non-aqueous phase was injected onto a 30-m DB17 megabore column under the following conditions: injection temperature 120 °C; oven temperature 90 °C; flame ionization detector at 120 °C. The amount of anaesthetic in each sample was determined from the peak height against a standard curve for the agent. All experiments in which polarization anisotropy was measured were performed under steady state conditions to ensure equilibration of the anaesthetics. Pre-equilibration was for 15 min for enflurane, halothane, isoflurane and desflurane, and 60 min for methoxyflurane and trichloroethylene. Nitrous oxide was delivered with oxygen from a Boyles anaesthetic machine for 15 min. Control samples were exposed to air or oxygen only, as appropriate, for the same period.

DPH (in tetrahydrafuran) and TMA-DPH (in dimethylformamide) were added to erythrocyte ghost membranes to final concentrations of 0.5 and 5 μmol $litre^{-1}$, respectively, and incubated for 30 min at 37 °C with gas delivery as before. Addition of solvent from the stock solution never exceeded 0.05%. Fluorescence polarization anisotropy, as a measure of the degree of depolarization of the emitted signal, was measured in duplicate at 37 °C using a Perkin-Elmer LS50 luminescence spectrofluorimeter. Excitation and emission wavelengths were 365 nm and 456 nm. Background fluorescence from unlabelled membrane samples, which was always less than 3% of the total signal, was subtracted from measurements in which probes were incorporated. All measurements were made in duplicate. Under vertical polarized light excitation (subscript V), fluorescence polarization anisotropy was defined by the equation:

$$r=\frac{(I_{\parallel}-I_{\parallel}{}^{S})_V-G(I_{\perp}-I_{\perp}{}^{S})_V}{(I_{\parallel}-I_{\parallel}{}^{S})_V+2G(I_{\perp}-I_{\perp}{}^{S})_V}$$

with a correcting grating factor, to correct for differences in instrument sensitivity for emitted polarized light in the parallel and perpendicular planes, measured on each sample of:

$$G=\frac{(I_{\parallel})_H}{(I_{\perp})_H}$$

where subscript H=horizontal polarized light excitation, and subscripts || and ⊥=components of the emitted light, parallel and perpendicular to the direction of polarization of the excitation beam. Superscript S=contribution of scattered light determined for an unlabelled reference sample of the same composition. Experiments were performed on erythrocytes from 4–10 subjects for each concentration of anaesthetic studied.

### PROTEIN DETERMINATION

Protein concentration was measured by the method of Lowry and colleagues.[18]

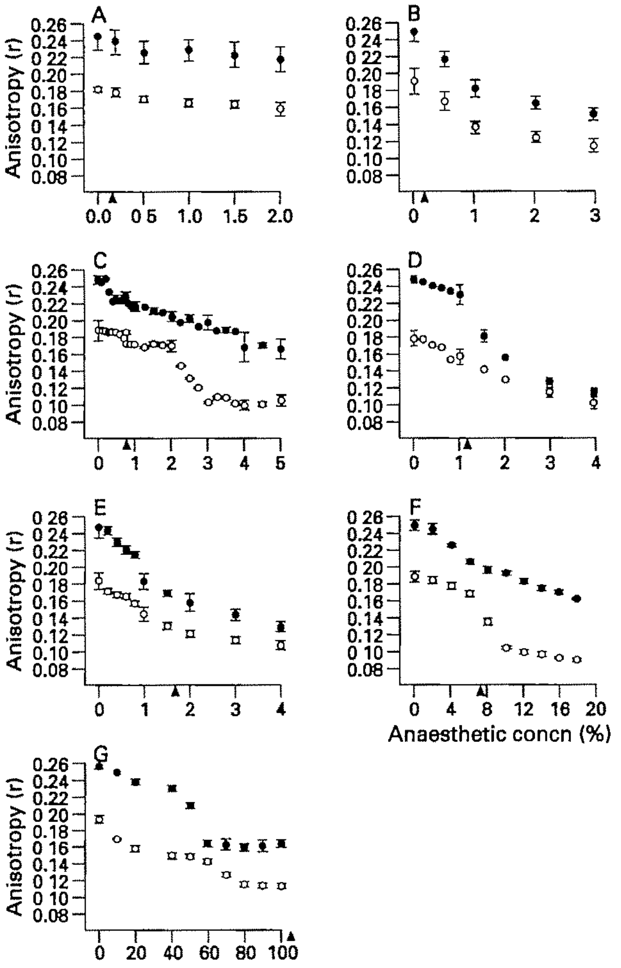

*Figure 1* Dose–response relationships between the fluorescence polarization anisotropy of membrane incorporated DPH (○) and TMA-DPH (●) and the concentration of volatile anaesthetic. A: Methoxyflurane; B: trichloroethylene; C: halothane; D: isoflurane; E: enflurane; F: desflurane; and G: nitrous oxide. Values of anisotropy are mean (SD). Experiments were performed on erythrocytes from 4–10 subjects for each concentration of anaesthetic. The minimum alveolar concentration (MAC) of each agent is shown by the arrow head. MAC values used were: methoxyflurane, 0.16%,[19] trichloroethylene, 0.17% (calculated),[20] halothane, 0.74%,[19] isoflurane, 1.15%,[21] enflurane, 1.68%,[22] desflurane, 7.25%[23] and nitrous oxide, 104%.[24]

## Results

Maximum concentrations of agents used in this study did not alter the wavelength of emission maxima or affect the intensity of emission of membrane incorporated probes in the analyses of fluorescence spectra. We conclude that depolarization measured in the presence of anaesthetic agents was a result of membrane disruption and not alteration of fluorescence life-time by quenching.

A dose-dependent decrease in the anisotropy of both DPH and TMA-DPH was observed over the clinically relevant range of concentrations studied for each agent (fig. 1). The shapes of the dose–response curves varied with each agent and with the distribution of the fluorophore in the membrane.

The ability of equipotent concentrations of agents

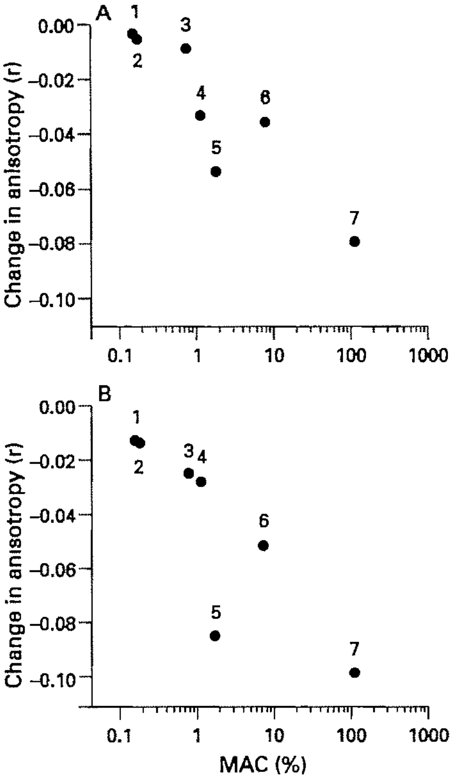

*Figure 2* Relationship between the change in fluorescence polarization anisotropy of erythrocyte ghost incorporated DPH (A) and TMA-DPH (B), measured at the minimum alveolar concentration (MAC) of the delivered agent, and anaesthetic potency (MAC). Anaesthetic agents: 1=methoxyflurane; 2=trichloroethylene; 3=halothane; 4=isoflurane; 5=enflurane; 6=desflurane and 7=nitrous oxide (anisotropy at 100% taken to approximate to MAC of 104%[24]). MAC values used are those given in figure 1.

*Table 1* Equilibration of volatile anaesthetic agents in 1 ml of Tris-HCl 10 mmol litre$^{-1}$ (pH 7.4) containing 100 µg of erythrocyte ghost protein ml$^{-1}$. The concentration of each agent delivered is given in parentheses. Data are mean (SEM) of three individual experiments

| Volatile anaesthetic | Half-life (min) |
|---|---|
| Trichloroethylene (0.2) | 1.8 (0.3) |
| Methoxyflurane (0.5) | 3.0 (0.2) |
| Halothane (0.75) | 1.8 (0.3) |
| Isoflurane (1.25) | 5.5 (1.8) |
| Enflurane (1.7) | 4.9 (0.2) |

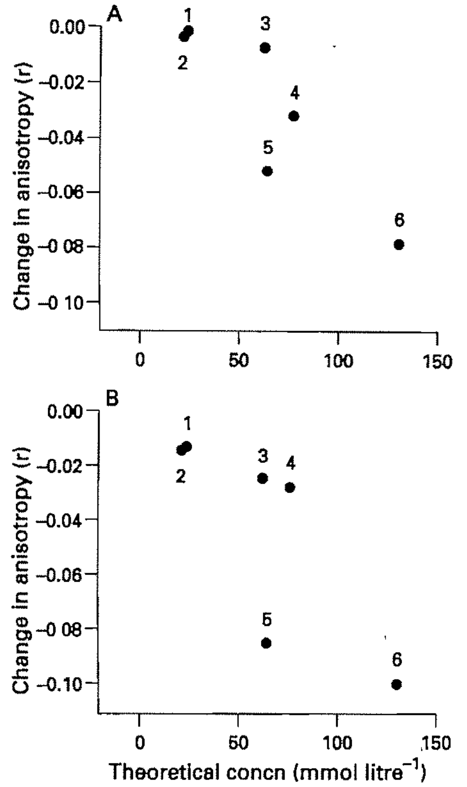

*Figure 3* Relationship between the change in fluorescence polarization anisotropy of erythrocyte ghost incorporated DPH (A) and TMA-DPH (B), measured at the minimum alveolar concentration (MAC) of the delivered agent, and the calculated theoretical concentration of agent in the membrane at MAC. Anaesthetic agents: 1=methoxyflurane; 2=trichloroethylene; 3=halothane; 4=isoflurane; 5=enflurane; 6=nitrous oxide (anisotropy at 100% taken to approximate to MAC of 104%[24]). MAC values used are those given in figure 1.

to perturb membrane microviscosity was assessed by comparing the change in anisotropy of the two membrane incorporated probes at the concentration of agents that produces anaesthesia in 50% of a population, $ED_{50}$ (minimum alveolar concentration, MAC). Values for the change in anisotropy at MAC were derived from the data in figure 1. An inverse relationship between the change in anisotropy of both membrane probes at MAC and anaesthetic potency was observed (fig. 2: DPH, correlation coefficient $r=-0.91$, $P<0.005$; TMA-DPH, $r=-0.85$, $P<0.02$). No other relationship between the potency and degree of membrane perturbation, for example the concentration of agent required to produce a defined change in anisotropy, was identified with either fluorescent probe.

Stable equilibrium between gaseous and aqueous phases at delivered gaseous concentrations of approximately 1 MAC was confirmed for five of the agents (table 1). A theoretical concentration of agent in the erythrocyte membrane at the MAC concentration of delivered gases was calculated,[12] using olive oil–gas partition coefficients where known (unknown for desflurane), and related to the change in anisotropy at MAC for each of the agents (fig. 3). A linear relationship between the change in anisotropy and theoretical membrane concentration was observed for anisotropy determined with the DPH probe (correlation coefficient $r=-0.89$, $P<0.02$) but when TMA-DPH was used as probe this relationship only approached statistical significance ($r=-0.79$, $P=0.06$).

## Discussion

The identity of the primary site(s) of action of volatile anaesthetic agents remains to be determined. There has been much discussion on whether or not an interaction in the membrane bilayer or a direct interaction with hydrophobic sites on target proteins is responsible for anaesthesia (reviewed in Aloia, Curtain and Gordon,[6] Miller,[8] Koblin[9] and Franks and Lieb[12 13]). Polarization anisotropy of the membrane incorporated fluorescent probes DPH and TMA- DPH in the presence of clinically relevant concentrations of volatile agents suggested that decreased membrane microviscosity is linked to changes in functional properties of the membrane.[14 25] To test if there is a relationship between anaesthetic potency and the ability of volatile anaesthetic agents to produce membrane perturbation, reflected by polarization anisotropy of membrane incorporated probes, the change in anisotropy of the probes DPH and TMA-DPH was investigated in this study for a range of volatile anaesthetic agents at clinically relevant concentration ranges. The erythrocyte membrane was used as a simple model biological membrane system with a defined composition and devoid of organelle membranes of varying composition that could have complicated interpretation. Although the magnitude of changes produced in the erythrocyte membrane may be quantitatively different, this membrane system would be expected to mirror changes that occur in other membranes that may have a more direct involvement in the mechanism of anaesthesia.

Using DPH and TMA-DPH to probe the core and outer regions of the bilayer, respectively,[15] we found that clinical concentrations of all agents produced a decrease in anisotropy consistent with decreased membrane microviscosity. The different shapes of the dose–response curves for alteration of membrane microviscosity obtained both for different agents and with respect to localization of the probe in the bilayer suggested complex and non-uniform interactions of the agents within the membrane. Contrary to the proposed hypothesis that equipotent clinical concentrations of volatile anaesthetics would produce a similar degree of membrane perturbation, the most potent anaesthetic agents produced the least change in anisotropy of probes at MAC concentrations. This series of observations indicates that there is no direct relationship between the ability of an agent to alter the anisotropy of membrane probes and anaesthetic potency and argues against a role for disruption of bulk phase membrane microviscosity in the transduction of the effect(s) of volatile anaesthetic agents to membrane mechanisms. These observations further suggest that links between membrane microviscosity and membrane function identified previously[14 25] are unrelated to anaesthetic action.

Dissociation of membrane perturbing effects and anaesthetic mechanism has been suggested previously in a study comparing the actions of

2-[2-methoxyethoxy]-ethyl 8-[cis-2-n-octylcyclopropyl]-octanoate ($A_2C$) and benzyl alcohol.[26] In common with benzyl alcohol, i.v. administration of $A_2C$ was found to perturb brain membranes but, unlike benzyl alcohol, $A_2C$ did not produce either intoxication or anaesthesia in mice. Both $A_2C$ and benzyl alcohol were found to inhibit [$^{35}$S]t-butylbicyclophosphorothionate (TBPS) binding and reduce muscimol- stimulated $^{36}Cl^-$ influx into brain vesicles at the same concentrations that reduced membrane order. However, at lower concentrations benzyl alcohol, but not $A_2C$, stimulated muscimol-activated $^{36}Cl^-$ influx. A two-site model was proposed in which the "perturbant" site responsible for decreased $^{36}Cl^-$ uptake was proposed to be distinct from an "anaesthetic" site responsible for augmentation of $^{36}Cl^-$ flux and anaesthesia.

From the inability to detect membrane perturbations at clinically relevant concentrations of volatile agents using several biophysical techniques,[27–30] it has been argued that the mechanism of anaesthesia of these agents does not involve acting as hydrophobic solutes to produce non-specific perturbation of bulk phase membrane properties and, hence, membrane protein function. Such conclusions presuppose that the chosen biophysical variable investigated reflects any membrane action of an anaesthetic, that a change in properties is observed within the time scale of the measurement and that the variable is sufficiently sensitive to demonstrate an interaction. As important as showing absence of anaesthetic effect at clinical concentrations is investigation of the significance of anaesthetic-induced membrane perturbations that have been reported at clinically relevant concentrations of volatile agents.[14 25] The inverse relationship between the ability to perturb membrane microviscosity and anaesthetic potency observed in this study suggests that links between membrane perturbation and membrane protein function reported previously[14 25] may be secondary phenomena, reflecting the presence of the anaesthetic molecules in the membrane rather than perturbations of relevance to the mechanism of anaesthesia.

As measurements were made at steady state between the gaseous and aqueous phases we were able to calculate a theoretical concentration of each agent in the lipid phase using olive oil–gas partition coefficients. Partition coefficients into lipid systems related to a phospholipid bilayer were not known for enough of the agents to allow this relationship to be calculated for a more representative lipid phase. Although partitioning of gases into olive oil and the erythrocyte membrane is unlikely to be identical, a proportionality in solubility between the two systems would be expected. Despite the differences in chemical structure between the anaesthetics, the change in anisotropy at the MAC concentration was proportional to the calculated theoretical concentration of agent in the lipid phase and, hence, the relative number of molecules of anaesthetic in the lipid bilayer. This correlation was highly significant with the DPH probe but only approached statistical significance for the TMA-DPH probe. Although several assumptions have been made in these calculations, it would appear that membrane microviscosity changes in the presence of volatile anaesthetic agents simply reflect the presence of anaesthetic molecules in the lipid membrane and are unrelated to the mechanism of anaesthesia.

In conclusion, our results are inconsistent with a role for perturbation in membrane microviscosity in the mechanism of anaesthesia of volatile agents. While perturbation of the dynamic properties of the bulk phase of the membrane may be unimportant, the ability of anaesthetic agents to dissolve in membrane bilayers may still prove to be important in their action.

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# Effect of propofol on isolated human omental arteries and veins

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## Summary

To elucidate the effect and mode of action of propofol on human vascular smooth muscle tension, we have investigated the effect of propofol alone and the effect of propofol on contractions induced by U46619, KCl and caffeine on isolated human omental vessels. Propofol $10^{-3}$ mol litre$^{-1}$ induced contractions in both arteries and veins attenuated the contraction elicited by U46619, KCl and caffeine in a concentration-dependent manner. The threshold concentrations for the effect of propofol in the artery were: $10^{-5}$ mol litre$^{-1}$ (U46619, caffeine) and $10^{-4}$ mol litre$^{-1}$ (KCl); and in the vein, $10^{-5}$ mol litre$^{-1}$ (U46619) and $10^{-4}$ mol litre$^{-1}$ (KCl, caffeine). We conclude that propofol at lower concentrations appeared to primarily attenuate contraction involving release of cellularly sequestered calcium. At higher concentrations ($>10^{-4.5}$ mol litre$^{-1}$), propofol appeared to affect contraction involving extracellular or intracellular calcium fluxes similarly. (*Br. J. Anaesth.* 1997; **78**: 296–300).

**Key words**
Anaesthetics i.v, propofol. Arteries, contraction. Veins, contraction. Ions, calcium.

Anaesthesia with propofol is accompanied by a reduction in arterial pressure.[1–4] This has been suggested to be caused by a decrease in either cardiac output (CO)[5], systemic vascular resistance (SVR),[6–10] or both.[1] The decrease in CO could be a result, at least in part, of a propofol-induced increase in venous capacitance.[4 11] Earlier studies suggest that the underlying mechanisms include both depression of sympathetic outflow[12 13] and a direct effect on the blood vessels or heart.[13]

An understanding of the mechanisms of the direct action of propofol on the blood vessel wall may be useful in the development of new anaesthetic agents with less tendency to induce hypotension during anaesthesia. Previous studies on vascular specimens have suggested that propofol decreases the contractility of vascular smooth muscle by modulating free cytosolic calcium availability. In the rat aorta,[14] atria and portal vein[15] and rabbit mesenteric arteries and veins,[16] propofol has been reported to act as a calcium channel antagonist and in isolated canine coronary arteries, propofol may act as a calcium channel agonist.[17] In the porcine coronary artery, propofol at low concentrations inhibits calcium influx, while propofol at higher concentrations ($10^{-4}$ mol litre$^{-1}$) also inhibits intracellular calcium release.[18] The relevance of the results from these experiments in humans is unclear. The aim of this study was to investigate the direct effects of propofol and the effect of propofol on contractions involving influx of extracellular calcium or release of cellularly sequestered calcium in isolated human omental artery and vein.

## Materials and methods

The study was approved by the Ethics Committee of the University of Lund.

Macroscopically normal segments of human omental arteries and veins were obtained from 36 patients, aged 29–88 yr (median 61 yr), undergoing abdominal surgery. Patients with endocrine tumours, abdominal infections and previous radiotherapy were excluded. The male/female ratio was 0.7. Experiments were performed within 48 h. The vessels, after being dissected free from fat and connective tissue, were stored in aerated Krebs–Ringer solution (KRS, composition see below) at +4 °C. Vessels were cut into 2–4-mm long ring segments and placed in 2-ml tissue baths on two L-shaped hooks, one of which was attached to a Grass FTO3C force displacement transducer for isometric measurement of tension. Vessel tension was recorded on a Grass polygraph model 7b. The baths were maintained at 37 °C and contained KRS, which was aerated continuously with 88.5% oxygen and 11.5% carbon dioxide, to give pH 7.4, $P\text{CO}_2$ 5.0 kPa and $P\text{O}_2$ approximately 40 kPa.

The artery and vein segments were stretched gradually to a resting tension of 6 mN during a 60–90-min equilibration period, to obtain the previously determined optimal resting tension level. After the equilibration period, KCl 90 mmol litre$^{-1}$ was added to the baths repeatedly (2–4 times), each time followed by washout, until consistent contractions were elicited. For each vessel segment, the greatest contraction elicited was used as a contraction reference. Contractile responses are given as percentages of this contraction reference.

In the first series of experiments, propofol was added cumulatively ($10^{-9}$–$10^{-3}$ mol litre$^{-1}$) to the

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organ baths at 10-min intervals to allow the segments to respond to each concentration. Every 20 min KRS was changed. Control experiments with the corresponding concentrations of the propofol solvent dimethylsulphoxide (DMSO) were performed in parallel.

In the second series of experiments, the dependence of extracellular calcium for the action of KCl and the stable thromboxane $A_2$ analogue, U46619, was determined. The two contractors (KCl 90 mmol litre$^{-1}$ and U46619 $10^{-10}$–$10^{-5}$ mol litre$^{-1}$ in log units cumulatively) were added to vessel segments in organ baths containing either KRS or calcium-free KRS ($Ca^{2+}$-free KRS, composition see below) and the resulting contraction recorded.

In the third series of experiments, we investigated the influence of propofol on contractions induced by KCl in KRS and U46619 in $Ca^{2+}$-free KRS. Tissues were preincubated with a propofol concentration of either $10^{-6}$, $10^{-5.5}$, $10^{-5}$, $10^{-4.5}$, $10^{-4}$, $10^{-3.5}$ or $10^{-3}$ mol litre$^{-1}$ for 10 min. The buffer solution was then changed, the same concentration of propofol was added again, and KCl $10^{-3}$–$10^{-1}$ mol litre$^{-1}$ in 0.5 log units cumulatively or U46619 $10^{-10}$–$10^{-5}$ mol litre$^{-1}$ in log units cumulatively was added. The resulting contraction was recorded. Control experiments with vessel segments exposed to equal concentrations of the propofol solvent DMSO were also performed.

In the fourth series of experiments, we investigated the influence of propofol on the release of cellularly sequestered calcium. Tissues were preincubated with propofol at concentrations of $10^{-5}$, $10^{-4.5}$, $10^{-4}$ or $10^{-3.5}$ mol litre$^{-1}$ for 10 min. $Ca^{2+}$-free KRS was used. The buffer solution was then changed, and the same concentration of propofol was added in addition to caffeine 20 mmol litre$^{-1}$. The resulting contraction was recorded. Control vessels exposed to DMSO were performed in parallel.

### STATISTICAL ANALYSIS

Values are expressed as mean (SEM). The Student's *t* test was used for statistical evaluation. $P<0.05$ was considered statistically significant and only significant differences are given in the text. When similar experiments were performed on more than one segment from the same patient, the mean for each patient was calculated before presentation and statistical analysis. The number of patients is indicated by *n*.

### PHARMACOLOGICAL AGENTS

The following compounds were used: propofol (Research Biochemicals International, RBI); 9,11-dideoxy-11,9-epoxy-methanoprostaglandin $F_{2\alpha}$ (U46619, Sigma); caffeine (KEBO Lab); disodium-calcium EDTA (Sigma); dimethylsulphoxide (DMSO, Sigma); ethylene glycol-bis(β-amino-ethylether) N,N,N',N'-tetraacetic acid (EGTA, Sigma). The compounds were dissolved and diluted in distilled water, except for propofol, which was dissolved in DMSO and diluted in distilled water. Krebs–Ringer solution (KRS) contained (mmol litre$^{-1}$): $Na^+$ 143, $K^+$ 4.6, $Cl^-$ 126.4, $Ca^{2+}$ 2.5, $HCO_3^-$ 25.0, $Mg^{2+}$ 0.79, $SO_4^{2-}$ 0.79, $H_2PO_4^-$ 1.2, glucose 5.5 and EDTA 0.024. The calcium-free Krebs–Ringer solution ($Ca^{2+}$-free KRS) refers to KRS from which $Ca^{2+}$ 2.5 mmol litre$^{-1}$ and $Cl^-$ 5 mmol litre$^{-1}$ were omitted and EGTA 0.1 mmol litre$^{-1}$ was added. To ensure calcium-free solution in the organ baths, the baths were rinsed repeatedly with $Ca^{2+}$-free KRS for 15 min before the experiments.

## Results

When added cumulatively to the vessel segments, propofol was found to alter vessel tension in both artery and vein segments similarly. At concentrations less than $10^{-5}$ mol litre$^{-1}$, no change was seen, but at $10^{-5}$ and $10^{-4}$ mol litre$^{-1}$, vessel tension became increasingly unstable. At $10^{-3}$ mol litre$^{-1}$, contractions of 28 (10) % (artery, $n=3$) and 50 (5) % (vein, $n=3$) were seen. The propofol solvent DMSO, in equal amounts as in the propofol experiments, did not affect vessel tension (fig. 1).

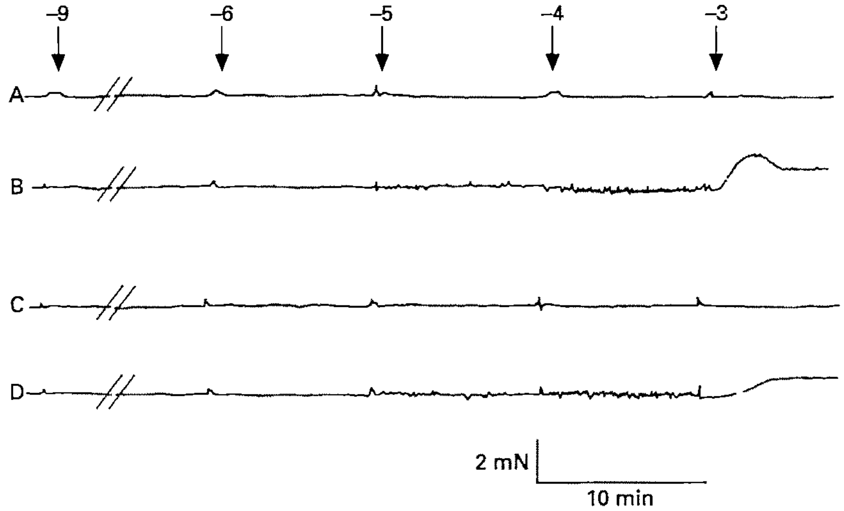

*Figure 1* Tracing of isometric tension in an isolated human omental artery segment in the presence of increasing concentrations of the propofol solvent DMSO (A) and propofol (B), and in a vein segment in the presence of increasing concentrations of DMSO (C) and propofol (D). DMSO was administered in concentrations equal to the concentration of DMSO in the corresponding propofol experiments.

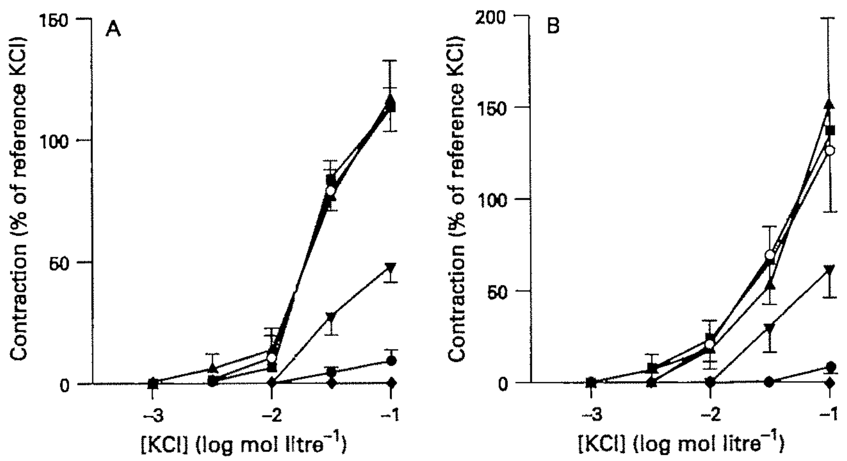

*Figure 2* A: Concentration–response curves for KCl in the absence of propofol (○, reference KCl contraction: 11.2 (2.7) mN, $n$=11) and in the presence of propofol $10^{-5}$ (■, reference KCl contraction: 12.0 (2.5) mN, $n$=11), $10^{-4\ 5}$ (▲, reference KCl contraction: 10.1 (2.7) mN, $n$=11), $10^{-4}$ (▼, reference KCl contraction: 10.7 (2.7) mN, $n$=11), $10^{-3\ 5}$ (●, =reference KCl contraction· 12.0 (2.8) mN, $n$=8) or $10^{-3}$ (◆, reference KCl contraction: 5.6 (2.6) mN, $n$=4) mol litre$^{-1}$ in human omental arteries. Values are mean (SEM). B: Concentration–response curves for KCl in the absence of propofol (○, reference KCl contraction: 6.0 (2.1) mN, $n$=8) and in the presence of propofol $10^{-5}$ (■, reference KCl contraction: 7.1 (2.3) mN, $n$=8), $10^{-4\ 5}$ (▲, reference KCl contraction: 3.8 (1.0) mN, $n$=8), $10^{-4}$ (▼, reference KCl contraction: 6.6 (2 3) mN, $n$=8), $10^{-3.5}$ (●, =reference KCl contraction: 6.5 (2.1) mN, $n$=8) or $10^{-3}$ (◆, reference KCl contraction: 3.4 (1.2) mN, $n$=5) mol litre$^{-1}$ in human omental veins. Values are mean (SEM).

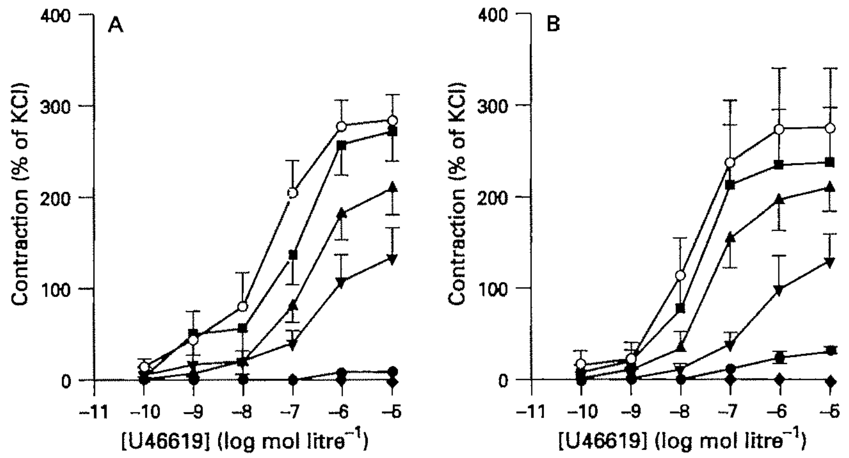

*Figure 3* A: Concentration–response curves for U46619 in Ca$^{2+}$-free KRS in the absence of propofol (○, reference KCl contraction: 6.9 (1.6) mN, $n$=10) and in the presence of propofol $10^{-5}$ (■, reference KCl contraction: 7.0 (1.6) mN, $n$=9), $10^{-4\ 5}$ (▲, reference KCl contraction: 9.0 (2.5) mN, $n$=10), $10^{-4}$ (▼, reference KCl contraction: 5.6 (1.5) mN, $n$=9), $10^{-3\ 5}$ (●, =reference KCl contraction: 6.4 (2.0) mN, $n$=6) or $10^{-3}$ (◆, reference KCl contraction: 8.0 (2.3) mN, $n$=6) mol litre$^{-1}$ in human omental arteries. Values are mean (SEM). B: Concentration–response curves for U46619 in Ca$^{2+}$-free KRS in the absence of propofol (○, reference KCl contraction: 3.7 (0.8) mN, $n$=6) and in the presence of propofol $10^{-5}$ (■, reference KCl contraction: 4.9 (0.7) mN, $n$=6), $10^{-4\ 5}$ (▲, reference KCl contraction: 4.3 (1.1) mN, $n$=6), $10^{-4}$ (▼, reference KCl contraction: 4.3 (1.6) mN, $n$=6), $10^{-3.5}$ (●, =reference KCl contraction: 4.7 (1.8) mN, $n$=6) or $10^{-3}$ (◆, reference KCl contraction: 2.7 (1.1) mN, $n$=6) mol litre$^{-1}$ in human omental veins. Values are mean (SEM).

KCl contracted vessel segments in organ baths containing KRS. No contraction occurred in segments in baths containing Ca$^{2+}$-free KRS (artery: $n$=3, vein: $n$=3). Contraction induced by KCl was not affected by propofol at concentrations less than $10^{-4}$ mol litre$^{-1}$. At this concentration the contractile response induced by KCl was diminished. In the presence of propofol $10^{-3.5}$ mol litre$^{-1}$ the contractile response was further attenuated. The contraction induced by KCl was abolished in the presence of propofol $10^{-3}$ mol litre$^{-1}$. Artery and vein segments behaved similarly (fig. 2). DMSO, in equal concentrations as in the propofol experiments, did not affect KCl-induced contraction (artery: $n$=3, vein: $n$=3).

U46619 induced similar contractions in artery and vein segments, irrespective of the medium present in the baths (KRS or Ca$^{2+}$-free KRS, data not shown; artery: $n$=5, vein: $n$=3). All subsequent experiments with U46619 were performed in Ca$^{2+}$-free KRS. Propofol at concentrations of $10^{-6}$ and $10^{-5\ 5}$ mol litre$^{-1}$ (not shown, artery: $n$=3, vein: $n$=4) did not affect U46619-induced contraction. At higher concentrations of propofol, the contraction induced by U46619 was attenuated in a concentration-dependent manner and was abolished completely at the highest concentration tested ($10^{-3}$ mol litre$^{-1}$, fig. 3). DMSO, in equal amounts as in the propofol experiments, did not alter U46619-induced contraction (artery: $n$=9, vein: $n$=7).

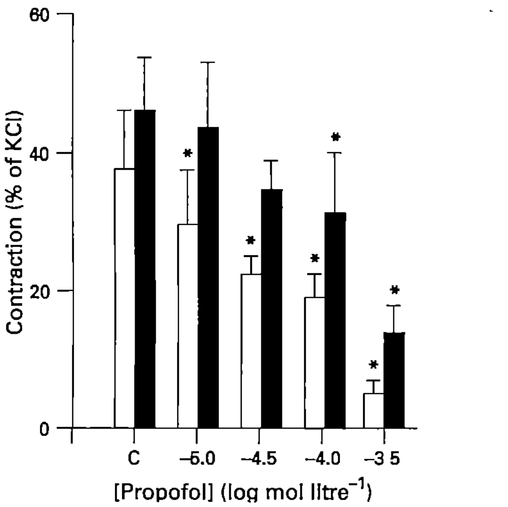

*Figure 4* Effect of propofol on contractions induced by caffeine 20 mmol litre$^{-1}$ in $Ca^{2+}$-free KRS in human omental arteries (□) and veins (■), $n$=6–7. *$P<0.05$ compared with control (C) (Student's $t$ test). Values are mean (SEM).

Caffeine-induced contraction was attenuated by a propofol concentration of $10^{-5}$ mol litre$^{-1}$ (artery) and $10^{-4}$ mol litre$^{-1}$ (vein). At higher concentrations of propofol, contraction was further attenuated (fig. 4).

## Discussion

This study supports the theory that changes in systemic vascular resistance contribute to propofol-induced hypotension, as propofol attenuated KCl-, U46619- and caffeine-induced contractions in human omental arteries. This is consistent with several measurements *in vivo* in both humans[1 6 8–10] and rats.[2] Vein segment contractions were also affected by propofol. This indicates that propofol may interfere with regulation of vessel tone on both the arterial and venous side of the circulation. This is consistent with *in vivo*[4 11] and *in vitro* studies,[19] but it contrasts with the findings of Baraka and colleagues,[8] who could not detect a change in venous reservoir during cardiopulmonary bypass. Different methods being used, for example *in vivo* and *in vitro* studies, and regional and species differences may explain the various findings.

An increase in cytosolic calcium is necessary for smooth muscle contraction. This may be achieved either by influx of calcium via specific channels in the cell membrane, by release of cellularly sequestered calcium or by a combination of these mechanisms. Our study showed that KCl-induced contraction in human omental arteries and veins was totally dependent on influx of extracellular calcium, as KCl-induced contraction was abolished in $Ca^{2+}$-free KRS. In contrast, U46619-induced contraction appeared to be mediated to a major extent via release of cellularly sequestered calcium, as changing KRS to $Ca^{2+}$-free KRS did not alter the concentration–response curve for U46619 in the artery or vein segments.

The lowest concentration of propofol which depressed U46619-induced contraction in $Ca^{2+}$-free KRS in both artery and vein segments was $10^{-5}$ mol litre$^{-1}$. KCl-induced contraction was unaffected by propofol at this concentration and a concentration of $10^{-4}$ mol litre$^{-1}$ was required to attenuate KCl-induced contraction. Thus propofol appeared to be more potent in inhibiting U46619-induced contraction than contractions elicited by KCl. These results suggest that propofol at the lowest effective concentration mainly modulated intracellular calcium release.

U46619 contracts smooth muscle primarily via $IP_3$-mediated calcium release from intracellular stores,[20] while caffeine primarily activates ryanodine receptors, thereby releasing calcium from these stores.[21] Both these mechanisms seem to be functional in vascular smooth muscle cells,[22] but they might not be two distinct processes. In the artery both U46619- and caffeine-induced contractions (i.e. probably both $IP_3$- and ryanodine receptor-mediated calcium release) were inhibited by propofol $10^{-5}$ mol litre$^{-1}$. In contrast, in the vein, propofol at this concentration appeared to interact only with $IP_3$-mediated intracellular calcium release.

Our results cannot easily be extrapolated to the *in vivo* situation. Concentrations of vasoactive compounds at their site of action are difficult to determine. The lowest effective propofol concentration in this study ($10^{-5}$ mol litre$^{-1}$) might be greater than the greatest concentration achieved during anaesthesia (cf. Park, Lynch and Johns[23]). Thus the clinical relevance of these findings remains to be determined.

At propofol concentrations of $10^{-4}$ mol litre$^{-1}$ and higher, contractions induced by all three contractors (U46619, caffeine and KCl) were attenuated. When added cumulatively to resting vessel segments, propofol at a concentration of $10^{-3}$ mol litre$^{-1}$ caused a small contraction. These effects of propofol may not be clinically important.

The study of Kamitani and colleagues[16] suggests that propofol interacts with endothelium-dependent mechanisms. The endothelium may actively interact with contractions in human omental arteries and veins.[24] In this study we have used endothelium intact vessel segments in order not to deviate too much from *in vivo* conditions. This implies that no conclusions can be drawn on the involvement of the endothelium in the action of propofol.

In summary, we have shown that propofol attenuated release of cellularly sequestered calcium in omental arteries and veins, which resulted in reduction in vessel tone. At higher concentrations of propofol a contraction-attenuating effect of a different nature appeared which was non-specific with regard to extra- or intracellular calcium fluxes.

## Acknowledgements

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*British Journal of Anaesthesia* 1997; 78: 301–307

# Differential effects of clonidine and dexmedetomidine on gastric emptying and gastrointestinal transit in the rat†

T. Asai, W. W. Mapleson and I. Power

## Summary

We have studied the effect of clonidine, dexmedetomidine and morphine on gastric emptying and gastrointestinal transit in the rat. In one group, each agonist was injected i.p. in 6–12 male Wistar rats. In another group of rats, yohimbine, naloxone or saline was injected with an agonist. At 30 min, radiolabelled saline 1 ml was infused into the stomach. At 1 h, gastric emptying and gastrointestinal transit were calculated by measuring the radioactivity in the gastrointestinal tract. We found that clonidine and dexmedetomidine strongly inhibited gastrointestinal transit ($ED_{50}$ 0.08 and 0.04 mg $kg^{-1}$, respectively). They also significantly inhibited gastric emptying ($P<0.05$), but the effect was weak (95% confidence intervals for difference from saline 8.2–34.9% with clonidine 1 mg $kg^{-1}$ and 3.4–15.4% with dexmedetomidine 0.03 mg $kg^{-1}$). Morphine strongly inhibited both gastric emptying and gastrointestinal transit ($ED_{50}$ 2.8 and 1.2 mg $kg^{-1}$, respectively). Yohimbine significantly antagonized the inhibitory effects of clonidine and dexmedetomidine ($P<0.05$), whereas naloxone, which significantly antagonized the effect of morphine ($P<0.01$), did not antagonize the effect of either of the other agonists. (*Br. J. Anaesth.* 1997; **78**: 301–307).

**Key words**
Gastrointestinal system, gastric emptying. Sympathetic nervous system, adrenergic agonists.

Delayed gastric emptying may induce several complications during the perioperative period. In critically ill patients, gastric emptying and intestinal transit are often delayed and this delay may cause pulmonary infection and bacterial overgrowth in the gastrointestinal tract.[1]

Opioids have been used widely in the perioperative period and in intensive care units, but they markedly delay both gastric emptying and intestinal transit.[2 3] However, we have been unable to trace any report of the $ED_{50}$ of morphine in inhibiting gastric emptying; therefore, the relative potency of opioids on gastric emptying and intestinal transit is not known.

$Alpha_2$ adrenoceptor agonists, such as clonidine or dexmedetomidine, reduce anxiety, induce sedation and produce analgesia.[4 5] They also decrease the amount of opioid and inhalation agent needed for induction and maintenance of anaesthesia while providing haemodynamic stability.[4 5] $Alpha_2$ agonists produce less respiratory depression, nausea and vomiting or pruritus than opioids.[4 5] For these reasons, the use of $alpha_2$ adrenoceptor agonists as adjuncts to anaesthetics has received much attention recently.[4 5]

There have been several reports on the effects of $alpha_2$ adrenoceptor agonists on gastric emptying, but the results are inconclusive. In some studies, peripherally injected $alpha_2$ adrenoceptor agonists did not delay gastric emptying in rodents.[6–8] In other studies they delayed gastric emptying of liquids in the rat[9] and that of both solids and liquids in the dog.[10] In humans, oral clonidine did not significantly delay gastric emptying of either a solid meal[11] or liquids,[12] whereas lidamidine, which also has an $alpha_2$ adrenoceptor agonist effect, weakly delayed gastric emptying.[13] These differences might have been caused by selectivity of these drugs to receptors other than the $alpha_2$ adrenoceptor.

Dexmedetomidine, the dextro-stereoisomer of medetomidine, is a highly selective $alpha_2$ adrenoceptor agonist.[14] Binding studies have shown that the selectivity of medetomidine to the $alpha_2$ adrenoceptor over the $alpha_1$ adrenoceptor is 5–10 times greater than that of other $alpha_2$ adrenoceptor agonists, such as clonidine and detomidine.[15]

The first aim of this study was to examine the effect of clonidine, dexmedetomidine and morphine on gastric emptying and gastrointestinal transit of liquids in the rat. The second aim was to determine the receptor type involved in the effects of these agonists.

## Materials and methods

We used male Wistar rats, weighing 200–250 g. The study was conducted under the Animal (Scientific

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Procedures) Act 1986 (Home Office Licence PPL 40/954, PPL 40/1397). Before the experiment, rats were housed under standard controlled environmental conditions, with a 12-h light–dark cycle. The animals were fasted for 24 h, but they were allowed free access to water until 20–30 min before the start of the experiment. Each animal was kept individually in a wire-mesh cage to prevent coprophagy during fasting. All experiments were started between 10:00 and 11:00. Dexmedetomidine (Orion-Famos Pharmaceuticals, Finland), clonidine, morphine and yohimbine (Sigma Chemical Co., UK) were prepared freshly on each day of experiment.

A group of six rats was allocated for each set of circumstances. If more than one rat was excluded (see below), another group of six rats was used until a group was completed in which no more than one rat was excluded. Data from the non-excluded rats from all groups for each set of circumstances (the number of rats ranged from 5 to 12) were used. However, we stopped after studying three rats for the highest doses of morphine and dexmedetomidine because of apparent complications (see results).

Gastric emptying and gastrointestinal transit were studied using radiolabelled sodium chromate,[16 17] which is minimally absorbed when infused into the stomach.[17] Clonidine 0.001–1.0 mg $kg^{-1}$, dexmedetomidine 0.0001–0.1 mg $kg^{-1}$, morphine 0.1–30 mg $kg^{-1}$ or saline, in a volume of 1.0 ml $kg^{-1}$, was given i.p. These doses were chosen on the basis of the reported $ED_{50}$ values for the antinociceptive effect of each drug (see discussion).

Thirty minutes later the rats were anaesthetized lightly with halothane. When the rat had become unconscious, saline 1.0 ml containing a radioactive marker (0.5 μCi (18.5 kBq) of chromium as the sodium salt ($^{51}Cr$ as $Na_2CrO_4$)) was given via a metal cannula into the stomach. The rat was allowed to recover from anaesthesia, which usually occurred within a few minutes.

Another 30 min later the rats were killed, the oesophagus just proximal to the gastric fundus and the duodenum just distal to the pylorus were cross-clamped, and the stomach and small intestine were removed. Twelve clamps were applied to the small intestine during gentle removal of the intestine to minimize the movement of contents. The intestine was placed on a ruled template and divided into 10 equal segments. The stomach and segments of intestine were placed into individual counting tubes.

Radioactivity in each segment was measured using an automatic gamma sample counter and counts per minute (cpm) obtained. Each sample was counted twice and mean cpm obtained. To obtain the control total count, 1.0 ml of radiolabelled saline was placed into a tube and the radioactivity counted. If there was chyme in either the stomach or small intestine, data were not used.

Gastric emptying of liquids was calculated as the percentage of radioactivity (cpm) which had entered the small intestine:

$$\%\text{gastric emptying } (\%\text{GE}) = ((\text{total cpm} - \text{stomach cpm}) \,/\, (\text{total cpm})) \times 100$$

From these values, percentage inhibition of gastric emptying was calculated from:

$$\%\text{inhibition of GE} = 100 \times (\text{control } \%\text{GE} - \text{test } \%\text{GE}) \,/\, \text{control } \%\text{GE}$$

where control %GE=mean %GE in the rats that received saline, and test %GE=%GE in each rat that received the test drug.

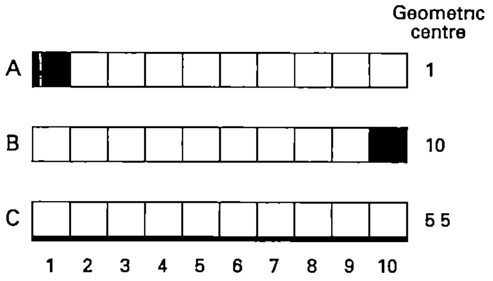

*Figure 1* Three hypothetical examples of the distribution of marker in the 10 segments of the small intestine. The distribution is expressed as "geometric centre" (the centre of gravity) ($=\Sigma(CiSi)/\Sigma Ci$, where Ci=count in segment Si)[16]: A: all the marker is in segment 1, therefore the geometric centre is 1 ($1\times1+0\times2+\ldots+0\times10=1$); B: all the marker is in segment 10, therefore the geometric centre is 10 ($0\times1+\ldots+0\times9+1\times10=10$); C: the marker is evenly distributed throughout the 10 segments, therefore the geometric centre is 5.5 ($0.1\times(1+2+\ldots+10)=5.5$).

Gastrointestinal transit was assessed using the "geometric centre" (the centre of gravity). This was calculated by a modification of a method described by Miller, Galligan and Burks[16] (fig. 1):

$$\text{geometric centre (GC)} = \Sigma(CiSi)/\Sigma Ci$$

where Ci=count in segment Si.

Percentage inhibition of gastrointestinal transit, expressed as the geometric centre (%GC), was calculated from:

$$\%\text{inhibition of gastrointestinal transit} = 100 \times ((\text{control GC} - \text{test GC}) \,/\, \text{control GC})$$

In the second part of the experiment, the receptor type involved in the inhibitory effect of the agonists was studied using yohimbine (an $alpha_2$ antagonist) and naloxone. The initial plan was to inject yohimbine, naloxone or saline with the $ED_{75}$ (see below) of each agonist. However, neither clonidine nor dexmedetomidine inhibited gastric emptying by greater than 50% (see results). Therefore, for clonidine, the $ED_{50}$ for antinociceptive effect (0.15 mg $kg^{-1}$)[18] was used; for dexmedetomidine, the second highest dose (0.03 mg $kg^{-1}$) was used as the $ED_{50}$ for antinociceptive effect in rats was not available. In another group of rats, gastric emptying and gastrointestinal transit after injection of either yohimbine or naloxone alone were studied.

### STATISTICAL ANALYSIS

The Mann–Whitney *U* test was used to compare gastric emptying and gastrointestinal transit between groups of rats which were subjected to different agonists or agonist–antagonist combinations. The values for all doses of clonidine or dexmedetomidine were pooled for this analysis. Either a Wilcoxon-type test for trend[19] (when two doses of an antagonist were used) or the Mann–Whitney *U* test (when one dose of an antagonist was used) was used to examine the effect of either yohimbine or naloxone on the inhibitory effect of agonist. $P<0.05$ was considered significant. The confidence intervals for medians

*Table 1* $ED_{50}$ (mg kg$^{-1}$) of clonidine, dexmedetomidine and morphine on gastric emptying and gastrointestinal transit (with 95% confidence limits). The $ED_{50}$ and upper 95% confidence limit were omitted when they were outside the range of doses used

| | Gastric emptying | Gastrointestinal transit |
|---|---|---|
| Clonidine | — | 0.080 |
| (*n*=41) | (4.6, —) | (0.049, 0.13) |
| Dexmedetomidine | — | 0.039 |
| (*n*=30) | (4.3, —) | (0.027, 0.065) |
| Morphine | 2.8 | 1.2 |
| (*n*=52) | (2.1, 3.8) | (0.87, 1.7) |

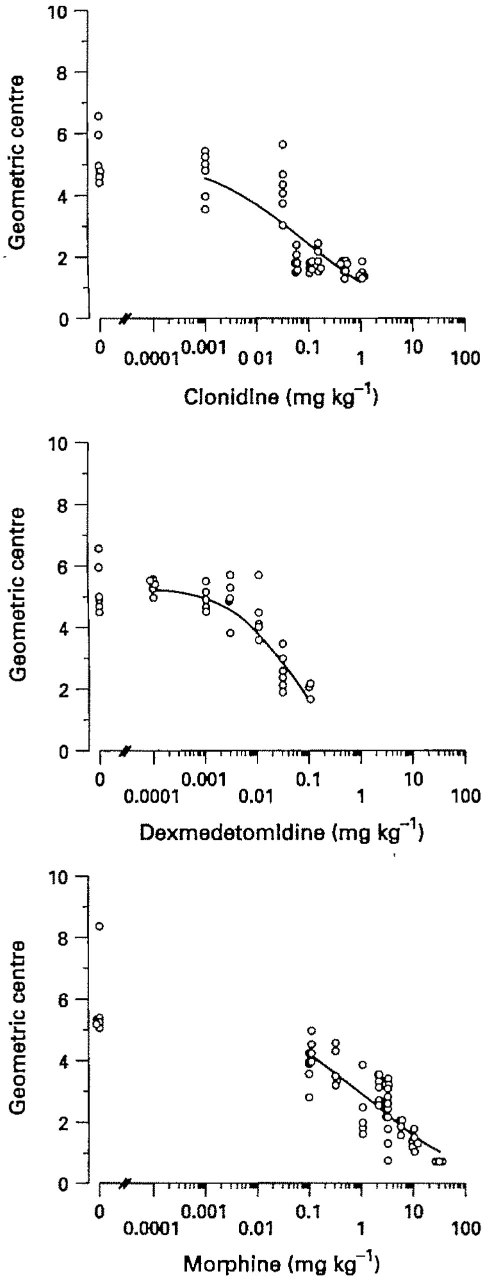

*Figure 2* Effect of clonidine (top), dexmedetomidine (middle) and morphine (bottom) on gastrointestinal transit. Saline 1 ml, containing a radiolabelled marker ($^{51}$Cr), was given 30 min after i.p. injection of drug. Gastrointestinal transit was examined 30 min later. A fitted logit dose–response curve is shown together with the value obtained from each rat (O). Symbols were displaced slightly on the *X* axis if there were similar values for any given dose. Values at zero dose are for the saline control.

were calculated using the SINTERVAL command (sign test) in Minitab Release 8.2 (running on Macintosh LC computer), which shows exact intervals for a stated confidence level close to 95%. Confidence intervals (CI) for the difference in gastric emptying between saline and an alpha$_2$ agonist were also calculated.

The variation in percentage inhibition with the dose of each agent was modelled by fitting a sigmoid logit curve to fractional inhibition against log dose. This was done (see appendix) using the statistical package GLIM (Generalized Linear Interactive

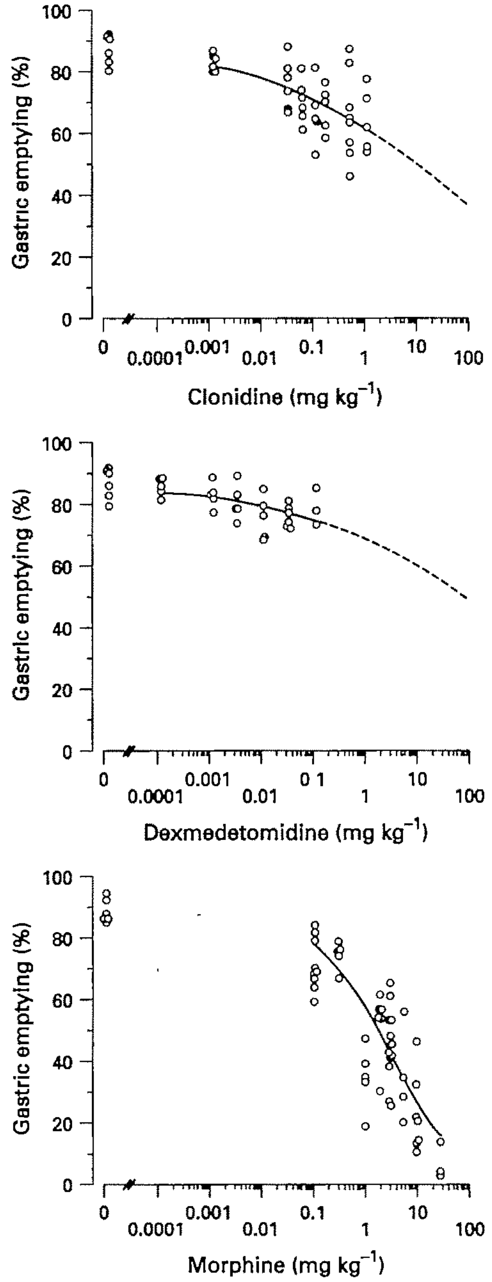

*Figure 3* Effect of clonidine (top), dexmedetomidine (middle) and morphine (bottom) on gastric emptying of a liquid. Saline 1 ml, containing a radiolabelled marker ($^{51}$Cr), was given 30 min after i.p. injection of drug. Gastric emptying was examined 30 min later. A fitted logit dose–response curve is shown together with the value obtained from each rat (O). Symbols were displaced slightly on the *X* axis if there were similar values for any given dose. The extrapolated parts of the curves for clonidine and dexmedetomidine are shown by a broken line. Values at zero dose are for the saline control.

*Table 2* Effect of yohimbine or naloxone on the inhibitory effect of clonidine, dexmedetomidine or morphine on gastric emptying and gastrointestinal transit of saline (median). *P* values were calculated using either the Wilcoxon-type test for trend[18] (when two doses of antagonist were used) or the Mann-Whitney *U* test (when one dose of antagonist was used), and 95% confidence limits (CL) of the difference between rats which received saline and those which received an antagonist are shown. Six to 12 rats were used for each group. [a]Antagonist effect; [b]additive effect

| | Gastric emptying | | | Gastrointestinal transit | | |
|---|---|---|---|---|---|---|
| | | Difference from saline group (0 dose of an antagonist) | | | Difference from saline group (0 dose of an antagonist) | |
| Treatment | Emptying (%) | CL | *P* | Geometric centre | CL | *P* |
| Clonidine 0.15 mg kg$^{-1}$ | | | | | | |
| +Saline | 70.9 | | | 2.0 | | |
| +Yohimbine 1.0 mg kg$^{-1}$ | 73.7 | [−3.3, 16.1] | 0.012[a] | 4.8 | [0.9, 3.3] | 0.046[a] |
| +Yohimbine 3.0 mg kg$^{-1}$ | 83.0 | [1.6, 24.1] | | 3.7 | [−0.5, 2.2] | |
| +Naloxone 1.0 mg kg$^{-1}$ | 63.1 | [−16.8, 3.6] | 0.014[b] | 1.7 | [−1.0, 0] | 0.081 |
| +Naloxone 3.0 mg kg$^{-1}$ | 51.5 | [−30.3, 0.9] | | 1.7 | [−1.0, 0.2] | |
| Dexmedetomidine 0.03 mg kg$^{-1}$ | | | | | | |
| +Saline | 78.0 | | | 2.5 | | |
| +Yohimbine 1.0 mg kg$^{-1}$ | 84.9 | [0.1, 10.7] | 0.01[a] | 5.1 | [0.9, 3 2] | 0.02[a] |
| +Yohimbine 3.0 mg kg$^{-1}$ | 83.1 | [1.4, 9.1] | | 5.7 | [1.2, 3.7] | |
| +Naloxone 1.0 mg kg$^{-1}$ | 64.2 | [−21.3, 3.2] | 0.12 | 1.9 | [−1.4, 0.4] | 0.13 |
| Morphine 13.4 mg kg$^{-1}$ | | | | | | |
| +Saline | 23.0 | | | 1.9 | | |
| +Naloxone 1.0 mg kg$^{-1}$ | 64.2 | [26.2, 51.7] | 0.003[a] | 2.6 | [0.2, 1.5] | 0.01[a] |
| +Yohimbine 1.0 mg kg$^{-1}$ | 34.8 | [−12.3, 28.1] | 0.15 | 1.6 | [−0.9, 0.6] | 0.58 |
| +Yohimbine 3.0 mg kg$^{-1}$ | 16.8 | [−19.8, 3.5] | | 1.2 | [−0.9, 0] | |
| Saline | | | | | | |
| +Saline | 88.2 | | | 4.9 | | |
| +Yohimbine 1.0 mg kg$^{-1}$ | 86.0 | [−12, 7.6] | 0.37 | 4.8 | [−1.5, 0.5] | 1.0 |
| +Yohimbine 3.0 mg kg$^{-1}$ | 82.8 | [−53.7, 8.2] | | 5.3 | [−1.1, 1.4] | |
| +Naloxone 1.0 mg kg$^{-1}$ | 71.7 | [−23.6, 8.4] | 0.02 | 4.9 | [−1.6, 1.0] | 0.20 |
| +Naloxone 3.0 mg kg$^{-1}$ | 72.2 | [−30.0, −2.5] | | 4.5 | [−2.1, 0.4] | |

Modelling), version 4,[20] update 8, running on a DEC mainframe computer under the Ultrix operating system (OSF/1 V2.OB). The output from the fitting process provided the information required to calculate $ED_{50}$ and $ED_{75}$ and, using the Fieller equation, the 95% confidence interval (CI) of those doses.[20 21]

## Results

Morphine 30 mg kg$^{-1}$ caused muscle rigidity; therefore, we stopped after studying three rats at this dose. Dexmedetomidine 0.1 mg kg$^{-1}$ caused strong sedation and apparent respiratory depression; therefore, we stopped after studying three rats. Clonidine 1.0 mg kg$^{-1}$ and dexmedetomidine 0.03 mg kg$^{-1}$ caused obvious sedation in all rats.

### GASTROINTESTINAL TRANSIT

Clonidine, dexmedetomidine and morphine inhibited gastrointestinal transit in a dose-dependent manner (fig. 2, table 1).

### GASTRIC EMPTYING

Morphine inhibited gastric emptying in a dose-dependent manner (fig. 3, table 1). In contrast, although clonidine significantly inhibited gastric emptying ($P=0.001$), the inhibitory effect was weak (95% CI for difference from saline 8.2–34.9% at the maximum dose of clonidine, 1 mg kg$^{-1}$) (fig. 3). Dexmedetomidine also weakly, but significantly, inhibited emptying ($P<0.05$; 95% CI for difference from saline 3.4–15.4% at the next-to-maximum dose, 0.03 mg kg$^{-1}$) (fig. 3).

### RECEPTOR TYPE

Yohimbine, an alpha$_2$ adrenoceptor antagonist,[22] significantly antagonized the inhibitory effect of clonidine and dexmedetomidine, but not that of morphine (table 2). Yohimbine itself at the doses used did not significantly affect either gastric emptying or gastrointestinal transit, although the rate of gastric emptying varied considerably after injection of yohimbine 3.0 mg kg$^{-1}$.

Naloxone itself significantly delayed gastric emptying, but not gastrointestinal transit (table 2). Despite its inhibitory effect, naloxone significantly antagonized the inhibitory effect of morphine (table 2). Naloxone did not significantly antagonize the effect of clonidine or dexmedetomidine; in fact, naloxone delayed gastric emptying further (table 2).

## Discussion

### DIFFERENCE IN THE EFFECTS BETWEEN ALPHA$_2$ AGONISTS AND MORPHINE

When the fitted curves for the effect of each drug on gastric emptying and gastrointestinal transit were plotted in terms of percentage of control values (fig. 4), it was apparent that morphine inhibited gastric emptying and gastrointestinal transit to a similar degree, whereas with clonidine and dexmedetomidine, inhibition of gastric emptying was much weaker than that of gastrointestinal transit. The ratio of the $ED_{50}$ values for gastrointestinal transit and

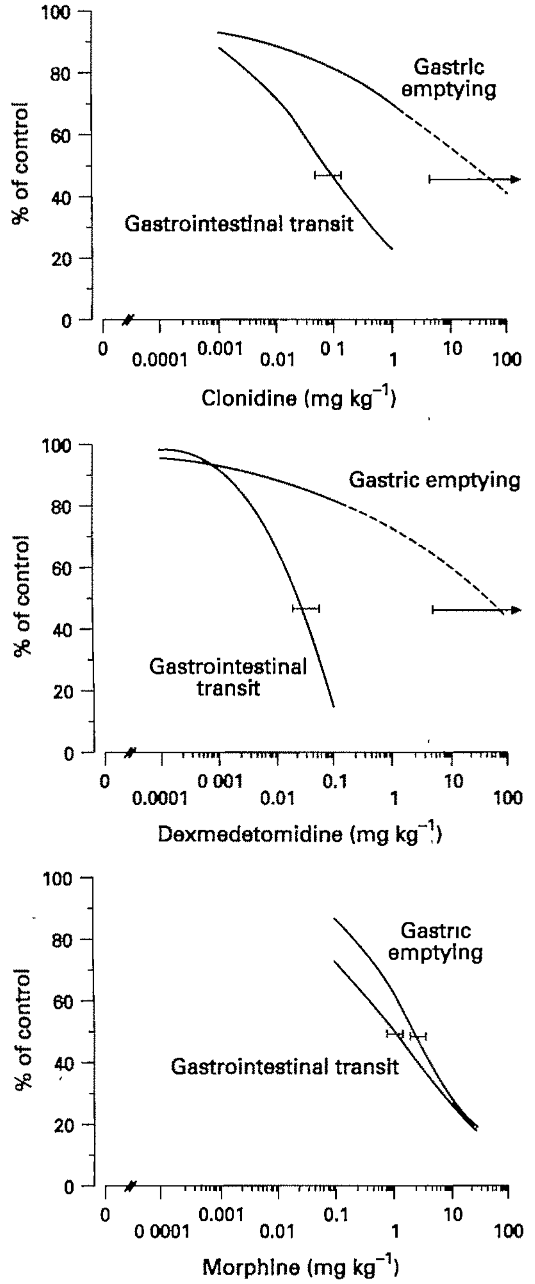

*Figure 4* Percentage gastric emptying and gastrointestinal transit of the control values for clonidine (top), dexmedetomidine (middle) and morphine (bottom). The extrapolated parts of the curves for clonidine and dexmedetomidine are shown by a broken line. The ED$_{50}$ and 95% confidence intervals are also shown.

gastric emptying was 2.3 for morphine but (by extrapolation) 365 for clonidine and infinity for dexmedetomidine.

The range of the reported ED$_{50}$ for the antinociceptive effect of morphine (table 3) includes the present ED$_{50}$ for gastric emptying (2.8 mg kg$^{-1}$). For clonidine and dexmedetomidine, however, the ED$_{50}$ values for antinociceptive effect (table 3) are very much less than the present ones for gastric emptying (lower limit of 95% CI: 4.6 mg kg$^{-1}$ for clonidine and 4.3 mg kg$^{-1}$ for dexmedetomidine). Therefore, it is unlikely that clonidine and dexmedetomidine at antinociceptive doses strongly inhibit gastric emptying, whereas it is likely for morphine.

There are several differences between alpha$_2$ adrenoceptor agonists and opioids in the mechanisms of their effects on gastric motility. First, alpha$_2$ adrenoceptor agonists inhibit the contraction of the stomach caused by stimulation of cholinergic neurones,[28–30] but not that induced by exogenous acetylcholine,[28 29] and these agonists may not lower the basal tone of the stomach.[28 30] In contrast, opioids strongly inhibit both basal and stimulated gastric motility.[31 32]

*Table 3* The reported ED$_{50}$ (mg kg$^{-1}$) for the antinociceptive effect of clonidine, dexmedetomidine and morphine injected either i.p. or s.c. in rats (unless specified). [a]The 0.05 mg kg$^{-1}$ produced 70% inhibition. [b]This value was obtained in mice; no data were available for rats

| | Type of nociceptive stimuli | ED$_{50}$ (mg kg$^{-1}$) | References |
|---|---|---|---|
| Clonidine | Thermal | 0.1–2.7 | [18, 23, 24] |
| | Chemical | 0.08–0.15 | [18, 23] |
| Dexmedetomidine | Thermal | <0.05[a] | [25] |
| | Chemical | 0.01[b] | [14] |
| Morphine | Thermal | 0.6–8 | [23, 26, 27] |
| | Chemical | 0.4–0.8 | [23, 26] |

Second, opioids increase pyloric pressure[33 34] leading to delay in gastric emptying. In contrast, alpha$_2$ adrenoceptor agonists either have no effect or relax the pylorus[35–37] and thus the pylorus does not impede emptying of gastric contents. However, a dilated pylorus may increase duodenogastric reflux,[37] and if so, net gastric emptying may be delayed. This may explain why there was a mild delay in gastric emptying after injection of clonidine and of dexmedetomidine in our study.

### POSSIBLE REASONS FOR DISCREPANCIES BETWEEN STUDIES

There have been two reports in which the effects of clonidine on gastric emptying of liquids were studied in the rat. Cooper and McRitchie found that clonidine 0.003–1.0 mg kg$^{-1}$ strongly inhibited gastric emptying of 5 ml of test liquid.[9] In contrast, Ruwart, Klepper and Rush found that clonidine up to 1.0 mg kg$^{-1}$ did not inhibit gastric emptying of 0.25 ml of test liquid, but strongly inhibited small intestinal transit.[6] The results of the Ruwart, Klepper and Rush study are similar to ours for clonidine using 1.0 ml of test liquid.

The reasons for the discrepancies between studies are not clear, but one possible cause is the difference in the volume of test liquids used. Because clonidine strongly inhibits intestinal transit, it is likely that the greater the volume of a test liquid infused into the stomach, the greater the pooling of the liquid in the duodenum. Distending the duodenum stimulates reflex relaxation of the stomach.[38–40] In the rat, distension of the duodenum by direct infusion with as little as 0.05 ml of saline relaxes the stomach, and the degree of gastric relaxation depends on the degree of distension of the duodenum.[38] Gastric emptying is delayed when the stomach is relaxed, because emptying is influenced by a pressure gradient between the stomach and the duodenum.[39] Cooper and McRitchie[9] infused a large volume of liquid (5 ml) into the stomach, whereas Ruwart, Klepper and

Rush[6] used a much smaller volume (0.25 ml); therefore, it is likely that the degree of distension of the duodenum and thus the degree of relaxation of the stomach would have been the greatest in the Cooper and McRitchie study[9] and least in the Ruwart, Klepper and Rush study.[6] Therefore, this may explain the marked delay in gastric emptying found in the study of Cooper and McRitchie[9] and the absence of delay in the Ruwart, Klepper and Rush study.[6]

The marked inhibition of gastric emptying in the study of Cooper and McRitchie[9], however, may not be physiological. We found that, when 5 ml of liquid were infused into isolated rat stomachs, there was marked distension and thinning of the gastric wall (unpublished observation). Thus the stomach was likely to be over distended in their study. In addition, increase in gastric volume relaxes the gastric tone[40 41] by stimulating the non-adrenergic, non-cholinergic vagal nerve.[42] These differences in the conditions of the stomach may also contribute to an explanation of the discrepancy.

### POSSIBLE CONFOUNDING FACTORS

We gave halothane to rats to insert an orogastric cannula. This might have affected the data. However, it is unlikely that halothane caused the difference in the transit between groups in our study, because halothane was used in both control and test groups, and also because the effect of clonidine and morphine was antagonized by yohimbine and naloxone, respectively.

It is also not clear if the inhibitory effect of clonidine and dexmedetomidine on gastric emptying and gastrointestinal transit is a direct effect or a secondary effect derived from other factors, such as decreased arterial pressure, heart rate or body temperature.

### GASTRIC EMPTYING AND GASTROINTESTINAL TRANSIT

In this study, clonidine and dexmedetomidine strongly inhibited transit in the small intestine, but only weakly inhibited gastric emptying. In contrast, atropine does not affect transit of liquids in the small intestine at doses that delay gastric emptying.[43] Caerulein, a cholecystokinin-like peptide, enhances intestinal transit but it either has no effect or even delays gastric emptying.[44] Furthermore, acoustic stress to mice accelerates gastric emptying without affecting gastrointestinal transit.[45] Thus it is likely that some of the mechanisms influencing gastric emptying are different from those influencing transit in the intestine.

### CLINICAL IMPLICATIONS

There are similarities between humans and rats in terms of the presence of opioid and $\text{alpha}_2$ adrenoceptor receptors in the gastrointestinal tract and in terms of behavioural effects (such as the antinociceptive effect) of opioids and $\text{alpha}_2$ agonists. Therefore, although the present $ED_{50}$ values cannot be transferred to humans, it is likely that, at antinociceptive doses, clonidine and dexmedetomidine would produce less inhibition of gastric emptying (relative to that on gastrointestinal transit) than does morphine.

In summary, we have shown that, in the rat, morphine inhibited both gastric emptying and gastrointestinal transit via opioid receptors to a similar degree, whereas clonidine and dexmedetomidine did so via $\text{alpha}_2$ adrenoceptors with only a weak inhibitory effect on gastric emptying, even at the maximum tolerable dose.

## Appendix

The method provided by the GLIM package, of fitting a sigmoid logit curve directly to the fractional inhibition, is usually used when each datum is in the form of *r* responders of a total of *n* subjects. The procedure assumes that the residuals conform to the binomial distribution in which the variance is a function of the fitted value of the proportion of individuals responding (*r/n*). Applying the process to fitting fractional inhibition in each rat resulted in residuals approximately 10 times greater on average than those of the binomial distribution; but this was compensated by using a scaling factor to correct for "over dispersion" as explained in the GLIM manual.[19] This implies the assumption that the variance of the residuals depended on the fitted proportion in the same way as in the binomial distribution—apart from the scaling factor. In other words, that the residuals were distributed in a manner proportional to the binomial distribution.

To test this assumption, the variance of the observed values from the fitted value was calculated for each dose of each agent, for both gastric emptying and gastrointestinal transit, including data from studies of two other agents, nalbuphine and pentazocine. This provided a total of 64 variances. The ratios of these variances to the corresponding binomial variances ranged from approximately 0.4 to 1 3 times the mean ratio—a range of approximately 3:1.

The data were also analysed using the conventional method of fitting a straight line to the logit of the fractional inhibition and assuming that the residuals were normally distributed. This implies that the variances were the same for all levels of inhibition; in fact they varied from 0.15 to 1.5 times the mean variance—a range of approximately 10:1.

Therefore, although the assumptions of the method we used were not entirely met, they were considerably more closely met, for our data set, than the assumptions involved in the conventional approach. It is also important to note that the $ED_{50}$ values from the conventional approach were all well within the 95% confidence limits of those obtained by the adopted method.

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SHORT COMMUNICATIONS

# Detection of inspiratory resistive loads after anaesthesia for minor surgery

G. B. DRUMMOND AND J. P. CULLEN

## Summary

We measured the ability to detect inspiratory resistances in 22 patients undergoing minor gynaecological surgery, using linear resistances of 1.2–24.4 cm $H_2O$ litre$^{-1}$ s, and ranked 1–9. The rank that could be detected was measured before surgery, approximately 10 min after recovery from anaesthesia, and then 25 min later. After anaesthesia there was a significant increase ($P<0.001$) in the rank number by 2, which returned to preoperative values 25 min later. Minute ventilation was reduced by 25% after operation and this may partly explain this change; however, we believe the transient decrease in ability to sense resistance indicates residual effects of anaesthetics and may explain in part the incidence of hypoxia caused by airway obstruction in patients after anaesthesia. (*Br. J. Anaesth.* 1997; **78**: 308–310).

**Key words**
Complications, airway obstruction. Hypoxaemia. Lung, respiratory resistance.

Episodes of hypoxaemia are common immediately after operation and are also frequent later, in association with treatment with opioids, where airway obstruction appears to be the cause.[1] Anaesthetic agents and opioids are known to reduce responses to hypoxia and hypercapnia but they may perhaps also reduce responses to other effects of airway obstruction. Such responses may be protective. For example, some patients with severe asthma have a reduced capacity to detect inspiratory resistance and have reduced responses to hypoxia. Such patients are more likely to suffer severe consequences in association with attacks of asthma, such as loss of consciousness or mechanical ventilation.[2] To assess the possibility that other responses to airway obstruction could be affected after anaesthesia, we tested the ability of patients to detect a threshold inspiratory resistive load before, immediately after and later after minor surgery with general anaesthesia.

## Methods and results

After obtaining local Ethics Committee approval and informed written consent, we recruited women undergoing minor gynaecological surgery as day-case patients. We noted any current medication, smoking history, a history of airway disease or exposure to pollutants, and also noted if the patient appeared unduly anxious.

We used a series of resistances constructed using different numbers of glass capillary tubes (6 cm long, of the type used for measuring erythrocycte sedimentation rate) mounted in parallel in a supporting tube. They were linear within 5% for flow rates of up to 30 litre min$^{-1}$ and had resistances of 1.2, 1.7, 2.5, 2.8, 3.8, 8.3, 10.3, 11.5 and 24.4 cm $H_2O$ litre$^{-1}$ s. Calibration was performed with a laboratory manometer system (for the purposes of statistical analysis, however, they were numbered 1–9 and considered as ranked values on an ordinal rather than an interval scale). Each resistance could be fitted in turn to a respiratory system.

The patient lay recumbent and wore a noseclip, and breathed from a mouthpiece connected to a unidirectional low resistance anaesthetic valve (Ambu Hesse). Valve resistance was 2 cm $H_2O$ litre$^{-1}$ s at an inspiratory flow rate of 3 litre s$^{-1}$. The inspiratory side of the valve was connected to a large bore three-way tap by means of a wide bore tube, 70 cm in length, so that a resistance could be added for a single inspiratory effort, unknown to the subject. She was asked to indicate by hand movement if she felt a change in the effort of breathing. The resistances were added each in turn until the patient reliably indicated it had been felt. The patient also breathed from the mouthpiece while minute volume and frequency were measured over 1 min with an electrical Wright respirometer (Ferrari) connected to the expiratory limb of the circuit. This device had been calibrated recently by the manufacturer.

The anaesthetic induction agent was restricted to propofol, but anaesthesia and surgery were not otherwise standardized. During and after surgery analgesics were given as judged necessary and all agents used were noted, including a plot of end-tidal concentration of the volatile agent *vs* time.

The minimum resistance detected, and minute volume and ventilatory frequency, were measured again immediately after recovery from anaesthesia, soon after the patient could co-operate with the test,

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and also after the patient had fully recovered and had returned to the ward. If the patient could not detect a resistance after recovery from anaesthesia, this response was scored as 10.

Data were analysed with the sign test and sign confidence limits to compare changes within patients with time, the Mann–Whitney test to compare subgroups, and descriptive plots using Minitab release 8 run in MS-DOS 6.2.

We recruited 25 patients but three did not complete the study. Of the remaining 22, one patient did not have measurements made in the ward. Mean age was 30 yr, height 160 (SD 7) cm and weight 62 (14) kg. Four patients reported mild asthma but none was currently receiving treatment. Nine were smokers and two were exposed to dust. Before anaesthesia minute volume was 8.7 (7.4–9.6) litre $\text{min}^{-1}$ and ventilatory frequency was 17 (13–19) bpm (median, quartiles). After recovery from anaesthesia the corresponding values were 6.3 (4.9–7.7) litre $\text{min}^{-1}$ and 15 (13–17) bpm, and on testing in the ward these values were 8.3 (6.4–9.2) litre $\text{min}^{-1}$ and 15 (14–17) bpm. Changes in ventilation were statistically significant ($P<0.001$ and 0.05, respectively), but changes in frequency were not.

The propofol dose used was 200 (165–300) mg, and duration of anaesthesia and surgery was 17.5 (10–21.5) min. The responses to loads were measured 11 (10–13) min after the end of anaesthesia. The tests in the ward were performed at 36 (30–42) min after the end of anaesthesia. Surgical procedures ranged from examination under anaesthesia to laparoscopic procedures. The anaesthetic techniques included intubation of the trachea, administration of neuromuscular blocking agents and morphine analgesia. However, the maximum duration of anaesthesia was only 25 min. Three patients received desflurane and the remainder enflurane, all in nitrous oxide, and the expired volatile agent concentrations were almost equipotent with no large variations in the concentrations administered. Seven patients received either fentanyl or alfentanil in small amounts and seven received morphine during operation.

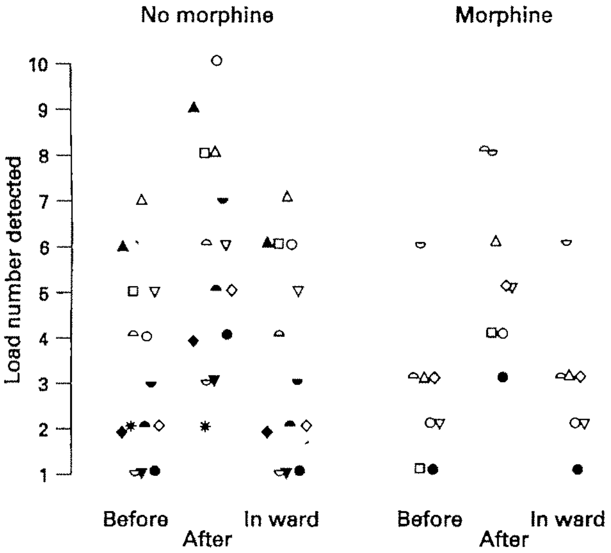

*Figure 1* Rank load number detected by each patient. Values are for before anaesthesia, immediately afterwards and after return to the ward. Patients who received morphine during surgery are shown separately and within each category each patient is represented by a different symbol.

The resistances detected are shown in figure 1. In each circumstance, patients were consistently able to identify a single load. Before operation the rank of resistance was median 2.5 (95% confidence intervals 2–4) and this increased to 5 (4–7) after operation and decreased to 3 (2–4) after return to the ward. The increase in resistance for detection after operation was significant ($P<0.001$) and there was no difference between the rank values before operation and after return to the ward.

There was no relationship between changes in minute volume and ventilatory frequency in individual patients, and the changes in detection of the load. The loads detected by patients who had received morphine in the intraoperative period (seven patients, median dose 15 (8–15) mg) were only greater by one rank, and 95% confidence limits for change in rank were almost identical. Two patients received topical anaesthesia to the trachea before intubation using lignocaine. They did not show excessive changes in load detection, the load detected increasing by two rank values in each case. No other factors associated with anaesthesia and surgery appeared to affect the resistance threshold. In particular, duration of surgery and time between i.v. induction agent and testing were not related to change in the rank of resistance detected.

## Comment

Appreciation of resistive loads is altered by changes in inspiratory flow rate.[3] After operation, mean inspiratory flow rate is likely to have been reduced by approximately 25% as expired minute volume was reduced by a median of 2.1 litre $\text{min}^{-1}$ from 8.6 litre $\text{min}^{-1}$, with no significant change in ventilatory frequency. This may have reduced the sensation of the resistance slightly but it is unlikely that this factor alone was responsible for the increase in load rank of 2.5. In addition, ventilation increased by only 1.1 litre $\text{min}^{-1}$ in the ward 30 min later and at this time load detection had returned to values found before operation. The resistive loads we used were not great: the greatest load in the series causes moderate dyspnoea in normal subjects (on a standardized linear verbal rank scale). Detection of a resistive load seems to be proportional to the proportional increase in resistance it generates (the Weber law)[3] and thus comparison of loads between subjects is of less value than changes in perception within subjects.

We measured the conscious appreciation of the load by the patient. This response may not reflect the response of the respiratory muscles to increased inspiratory resistance: there may continue to be an increase in muscle activation or force generation in response to the load, but conscious appreciation of the presence of the load is impaired.

The anaesthetic and surgical procedures that we studied were not standardized other than in the use of a single, relatively short-acting induction agent. In many respects the patients were heterogeneous, in terms of anxiety, postoperative pain and management (use of different opioids with various durations of action, and airway management by face mask, laryngeal mask or tracheal intubation). Further study of more uniform groups may allow factors responsible for the changes to be more established clearly, but this study did show a clear effect in a common clinical setting. The time course of the resolution of the effect suggests that the cause was residual anaesthetic agents. If this were the induction agent, the effect would be greater in patients who had short procedures: if it were the volatile agent then the effect would be more marked after the longer procedures. No such effects were evident.

Factors that protect patients from hypoventilation and resultant hypoxia, apart from vigilance of their attendants and oxygen therapy, are not well understood. The awake subject breathes with more force when inspiration is impeded but the influence of residual anaesthetic agents or opioids on detection and response to this response is not clear. Despite experimental evidence for responses to airway pressure, mediated by sensory information from the airways,[4] these responses seem to be inactive in sleeping humans. In sleeping subjects, airway obstruction causes increases in tongue muscle activity only after a complete respiratory cycle of obstruction. Then, airway muscle activity increases in parallel with activity in other respiratory muscles such as the diaphragm.[5] In fact, detection of airway resistance appears to be mediated by changes in intrapulmonary pressure.[6]

We conclude that after short periods of anaesthesia with relatively short-acting agents such as propofol, enflurane, and isoflurane, patients responded less well to minor transient airway obstruction, even when awake. The use of moderate amounts of opioids (morphine) did not appear to affect impairment, although we did not formally investigate this factor and patients who received morphine may have been systematically different from those who did not.

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# Does intrathecal fentanyl produce acute cross-tolerance to i.v. morphine?

D. W. COOPER, S. L. LINDSAY, D. M. RYALL, M. S. KOKRI, S. S. ELDABE AND G. A. LEAR

## Summary

We have examined the hypothesis that intrathecal fentanyl at operation can increase postoperative i.v. morphine requirements. We studied 60 patients undergoing Caesarean section. All received intrathecal 0.5% plain bupivacaine 2 ml combined with either fentanyl 0.5 ml (25 μg) (group F) (*n*=30) or normal saline 0.5 ml (group S) (*n*=30). In addition, 10 ml of an extradural solution (fentanyl 1 ml (50 μg) combined with 0.5% bupivacaine 9 ml ) was administered after delivery. Extradural solution was only given before delivery if the intrathecal injection failed to produce a block above T6 or the patient required further analgesia. Postoperative analgesia was provided with i.v. morphine patient-controlled analgesia. At operation, intrathecal fentanyl reduced the need to administer extradural solution before delivery, increased the anaesthetist's satisfaction with analgesia and reduced nausea, but increased pruritus. Up to 6 h after delivery there was no difference in postoperative morphine requirements or pain scores. Between 6 h and 23 h there was a 63% increase in morphine requirements in group F. We consider the most likely explanation for this finding to be that intrathecal fentanyl induced acute spinal opioid tolerance. (*British Journal of Anaesthesia* 1997; **78**: 311–313).

**Key words**
Anaesthetic techniques, extradural. Anaesthetic techniques, intrathecal. Anaesthesia, obstetric. Anaesthetics local, bupivacaine. Analgesics opioid, fentanyl. Analgesics opioid, morphine. Pain, postoperative. Potency, analgesic. Potency, drug, tolerance.

A prospective audit of postoperative i.v. patient-controlled analgesia (PCA) at our institute produced an unexpected observation. During the first 24 h after regional anaesthesia for Caesarean section, the dose of morphine was 47% greater for patients who had received intrathecal fentanyl at operation compared with those who had not. This led us to hypothesize that intrathecal fentanyl at operation can increase postoperative i.v. morphine requirements. In order to examine this hypothesis we have conducted a controlled study.

## Methods and results

This randomized, double-blind study was approved by the local hospital Ethics Committee. After obtaining informed consent we studied 60 ASA I–II patients undergoing morning elective Caesarean section.

Combined intrathecal and extradural analgesia was performed at L3–4 or an adjacent space. Patients received 0.5% plain bupivacaine 2 ml intrathecally combined with either fentanyl 0.5 ml (25 μg) (group F) (*n*=30) or normal saline 0.5 ml (group S) (*n*=30). The intrathecal solution was prepared by an anaesthetist who was not involved with patient management.

The extradural solution (10 ml) was prepared by combining fentanyl 1 ml (50 μg) with 0.5% bupivacaine 9 ml. This was administered between delivery and the end of operation when block regression would allow. Increments were only given before delivery if the intrathecal injection failed to produce a block above T6 or the patient required further analgesia. Additional extradural solution, consisting of 0.5% bupivacaine without fentanyl, could also be administered to achieve adequate block. If additional analgesia was needed after delivery then i.v. alfentanil was given as required. At the end of operation patients received rectal diclofenac 100 mg, unless contra-indicated. I.v. morphine was available via a disposable PCA device. This delivered a maximum bolus of 1 mg with a 5-min chamber refilling time. No more diclofenac was given before completion of the study at 10:00 on the first morning after operation.

At the end of operation the volume and timing of extradural solution given were recorded. The most severe pain experienced during operation was assessed using a visual analogue score for pain (VAS) (100-mm scale: 0=no pain, 100 mm=worst pain imaginable). The presence or absence of nausea, vomiting, pruritus and drowsiness during operation was assessed by the patient. Pruritus and drowsiness were graded as mild, moderate or severe. Both the anaesthetist and the patient made a verbal rating score (VRS) for satisfaction with analgesia during operation (0=excellent, 1=good, 2=fair, 3=poor).

The amount of morphine self-administered was

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*Table 1* Postoperative morphine requirements, pain scores and overall side effects (median (interquartile range) or percentage). *$P<0.05$ (Mann–Whitney); †$P<0.05$ (Kruskal-Wallis)

| | Morphine (mg h$^{-1}$) | | | | |
|---|---|---|---|---|---|
| | 0–3 h | 3–6 h | 6–23 h | | |
| Group F | 0.7 (0.0–2.0) | 2.7 (1.3–4.0) | 3.1 (1.9–4.8)* | | |
| Group S | 1.0 (0.2–2.0) | 2.7 (2.0–4.0) | 1.9 (1.5–2.3) | | |
| | Pain scores (mm) | | | | |
| | REC | 3 h | 6 h | 10 h | 23 h |
| At rest | | | | | |
| Group F | 0 (0–2) | 5 (0–15) | 26 (10–34) | 23 (7–34) | 30 (11–50) |
| Group S | 0 (0–8) | 3 (0–20) | 12 (1–25) | 23 (8–38) | 24 (5–30) |
| On coughing | | | | | |
| Group F | 1 (0–10) | 10 (1–27) | 33 (11–58) | 32 (14–56) | 33 (21–59) |
| Group S | 0 (0–11) | 16 (1–43) | 27 (21–44) | 34 (25–52) | 32 (21–57) |
| | Side effects (%) | | | | |
| | Nausea | Vomiting | Pruritus | Drowsiness | |
| Groups F/S | | | | | |
| During operation | 27/57 † | 7/20 | 60/7† | 43/20 $P=0.06$ | |
| In recovery (REC) | 7/3 | 0/0 | 63/13† | 40/20 $P=0.09$ | |
| REC–3 h | 10/7 | 3/4 | 63/41† | 47/26 | |
| 3–6 h | 17/14 | 7/0 | 30/34 | 62/59 | |
| 6–10 h | 34/41 | 14/21 | 38/43 | 79/56 | |
| 10–23 h | 35/27 | 14/12 | 69/65 | 83/59 | |

recorded at 3, 6 and 10 h after delivery and at 10:00 on the first morning after operation. VAS at rest and on coughing was recorded in recovery at 15 min after operation (REC), at 3, 6 and 10 h after delivery and at 10:00. Assessments of side effects were made in recovery and for the periods REC–3 h, 3–6 h, 6–10 h and 10 h–10:00. A VRS for satisfaction with postoperative analgesia was recorded at the end of the study.

A computer package (SPSS) was used for statistical analysis. Results were compared using Mann–Whitney and Kruskal–Wallis tests, with $P<0.05$ taken as significant.

Two groups of 30 patients were studied. They were matched for age, height, weight, previous Caesarean section, duration of operation, tubal surgery and duration of study. Group F received a similar total dose of extradural solution (median 10 (interquartile range (IQR) 10–10) ml) as group S (10 (IQR 10–10) ml). However, before delivery, less extradural solution was given in group F; 17% of group F received extradural supplementation (5 (IQR 3–11) ml) compared with 40% of group S (9 (IQR 5–10) ml) ($P<0.05$, Mann–Whitney). I.v. alfentanil was given to 7% of patients in group F compared with 23% in group S ($P=0.07$, Kruskal–Wallis). Median pain scores for the most severe pain experienced during operation were 0 (IQR 0–13) mm for group F and 6 (IQR 0–18) mm for group S ($P=0.07$, Mann–Whitney). The anaesthetist's satisfaction with operative analgesia was greater for group F (93% excellent, 3% good, 3% fair, 0% poor) than for group S (72% excellent, 17% good, 10% fair, 0% poor) ($P<0.05$, Kruskal–Wallis), but there was no difference in patient satisfaction with analgesia. Intrathecal fentanyl reduced nausea during operation but increased pruritus: 60% of group F were itchy (44% mild, 44% moderate and 11% severe) compared with 7% of group S (100% mild) (table 1).

Two patients in group F and one patient in group S did not receive diclofenac. Patients were studied for a mean of 23 h after delivery (table 1). Up to 6 h after delivery there was no difference in morphine requirements. Between 6 and 23 h after delivery morphine requirements were 63% greater for group F. There was no difference in postoperative pain scores, patient satisfaction with analgesia, nausea, vomiting or drowsiness. The increased pruritus with intrathecal fentanyl persisted into the early postoperative period.

## Comment

These results support the hypothesis that intrathecal fentanyl at operation can increase postoperative i.v. morphine requirements.

How could this be explained? If there was greater pre-emptive analgesia with intrathecal fentanyl it would have been expected to produce the opposite effect to that encountered. The most likely explanation is that intrathecal fentanyl produced acute opioid tolerance. Acute tolerance at the spinal level could increase systemic morphine requirements in two ways; first, by reducing the effect of morphine acting directly on spinal receptors; second, indirectly, by reducing the effect of endogenous spinal opioids. This could also reduce the effectiveness of supraspinal morphine acting via the descending pain control pathways.

Tolerance is a well recognized phenomenon that is dependent on dose of opioid and duration of exposure. With i.v. fentanyl acute tolerance can develop in dogs within 3 h.[1] Spinal opioids can also produce tolerance but it has not been considered to be a problem with short-term postoperative extradural or intrathecal use.[2]

High lipophilicity limits rostral spread after intrathecal administration. This can allow high concentrations of opioid at the spinal level without producing clinically significant respiratory depression or sedation. We believe that high spinal receptor occupancy with the potent opioid fentanyl produced acute tolerance after a single intrathecal dose. Nociceptive stimulation has been reported to inhibit the development of tolerance.[3] Local anaesthetic block and rectal diclofenac may therefore have contributed to the development of acute tolerance by reducing nociception. The use of extradural fentanyl may also have contributed to its development by increasing the total spinal dose.

Intrathecal fentanyl was beneficial at operation, reducing extradural anaesthetic requirements and increasing the anaesthetist's satisfaction with operative analgesia. Nausea was also reduced, probably because of more effective visceral afferent inhibition, but pruritus increased. After operation we found no benefits from intrathecal fentanyl. The lack of a difference in postoperative analgesia within the first 6 h was probably because both groups received extradural analgesia and rectal diclofenac.

We consider that this study provides evidence for a single dose of intrathecal fentanyl producing acute spinal opioid tolerance. This phenomenon clearly warrants further investigation. Our findings, in conjunction with a previous study which found no advantage from using more than 6.25 μg of intrathecal fentanyl,[4] have led us to reduce the total dose of spinal fentanyl given to Caesarean section patients.

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# Mechanism of femoral nerve palsy complicating percutaneous ilioinguinal field block

D. J. ROSARIO, S. JACOB, J. LUNTLEY, P. P. SKINNER AND A. T. RAFTERY

## Summary

Femoral nerve palsy has been reported after percutaneous ilioinguinal field infiltration with general anaesthesia for inguinal herniorrhaphy. The mechanism whereby this could occur was studied in cadaver dissections. It was found that the plane between the transversus abdominis muscle and the transversalis fascia was continuous laterally with the tissue plane deep to the iliacus fascia, which is the plane containing the femoral nerve. Injection of methylene blue 1 ml into this plane resulted in pooling of dye around the femoral nerve. Femoral nerve palsy may result from infiltration of a sufficient volume of local anaesthetic into the plane between the transversus abdominis muscle and the transversalis fascia with tracking of the injectate deep to the iliacus fascia to affect the femoral nerve. This finding has important implications for the performance of a percutaneous ilioinguinal field block particularly in day surgery provision. (*Br. J. Anaesth.* 1997; **78**: 314–316).

**Key words**
Anaesthetic techniques, regional, inguinal. Complications, nerve palsy.

Transient femoral nerve palsy (FNP) has been reported after percutaneous ilioinguinal field block (PIIFB) for inguinal herniorrhaphy.[1 2] In all cases discharge from hospital was delayed and serious injury was sustained by one patient.[2] The femoral nerve lies on the posterior abdominal wall covered by the strong iliacus fascia[3] and it is unlikely that simple diffusion of the local anaesthetic agent through tissue layers could result in FNP. Sufficient local anaesthetic to cause block must enter the plane deep to the iliacus fascia and there are potentially two routes whereby this may occur: (i) local anaesthetic is infiltrated directly under the iliacus fascia around the femoral nerve; (ii) local anaesthetic tracks around tissue planes to enter this plane and involve the femoral nerve.

This cadaver study was carried out in an attempt to elucidate the most likely mechanism whereby this complication could occur.

## Methods and results

We examined 21 cadavers with the abdominal contents removed in this anatomical study. In all cases the posterior and anterolateral abdominal walls had been left untouched and the parietal layers were exposed medially. A standard approach[4] to a PIIFB was used with a 22-gauge short bevel spinal anaesthetic needle inserted vertically through the skin at a point 3 cm medial to the anterior superior iliac spine (ASIS). The muscle and fascial layers traversed by the needle were observed and their thickness measured. The distance in the transverse axis between the femoral nerve and the point at which the vertically inserted needle made contact with the posterior abdominal wall was also measured. In three cases, sequential injections of methylene blue 1 ml were carried out first into the plane superficial to the transversus abdominis muscle and subsequently into the plane between that muscle and the transversalis fascia to examine the direction and extent of spread.

### ABDOMINAL WALL

The layers traversed in passing the needle from the anterior to the posterior abdominal wall are skin, subcutaneous fat, external oblique aponeurosis, internal oblique and transversus abdominis muscles, transversalis fascia, extraperitoneal fat, iliacus fascia and finally the iliacus muscle itself. In all cases the combined thickness of the internal oblique and transversus abdominis was less than 5 mm.

### DISTANCE FROM THE FEMORAL NERVE

Mean distance from the needle point to the femoral nerve along the posterior abdominal wall was 4.5 (95% confidence interval 0.3) cm in female cadavers ($n=11$) and 3.2 (0.3) cm in males ($n=9$). This difference between the sexes was highly significant ($P<0.0001$ Student's $t$-test).

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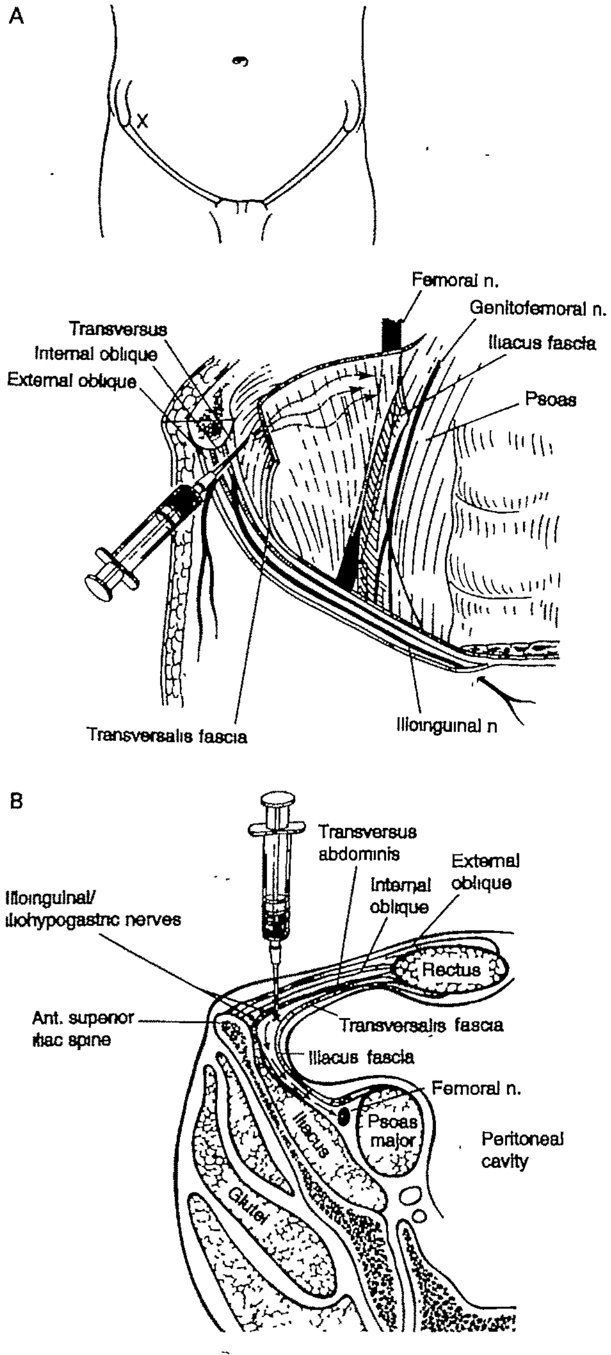

*Figure 1* A: Three-dimensional schematic representation of the body layers at the level of the anterior superior iliac spine and observed direction of spread of injectate after injection deep to the transversus abdominis muscle. B: Cross-sectional diagram of the pelvis at the level of the ASIS demonstrating reflection of the transversalis fascia as the iliacus fascia and the femoral nerve lying in the natural gutter lateral to the psoas.

### METHYLENE BLUE INJECTION

Injection of methylene blue 1 ml in the plane superficial to the transversus abdominis resulted in little dispersion of the injectate with discolouration remaining confined to the plane between that muscle and internal oblique. The transversalis fascia in all cases was continuous with and reflected laterally as the iliacus fascia (fig. 1). Injection of methylene blue 1 ml in the plane deep to the transversus abdominis involved advancement of the needle tip approximately 2–3 mm. Dye was seen consistently in all cases tracking medially and slightly cephalad under the iliacus fascia. Elevation of the iliacus fascia showed the dye pooling around the main trunk of the femoral nerve and other branches of the lumbar plexus.

## Comment

PIIFB is often used before inguinal herniorrhaphy as an adjunct to general anaesthesia to allow lighter anaesthesia in the perioperative period and for relief of postoperative pain. The technique carries morbidity as there have been five reported cases of prolonged FNP, with one patient suffering serious injury from a subsequent fall.[2] The incidence of FNP complicating PIIFB is uncertain but given the increasing trend towards day surgery provision, the incidence and associated morbidity of this complication, that is delayed ambulation, seems likely to increase. The ilioinguinal and iliohypogastric nerves lie initially between the transversus abdominis and the internal oblique, piercing the internal oblique at a variable distance medial to the ASIS to lie between the external oblique aponeurosis and internal oblique.[3] As segmental nerves (L1) they have a cutaneous distribution and also supply the parietal peritoneum; thus blockade of these nerves provides good analgesia after inguinal herniorrhaphy. The femoral nerve arises from the anterior rami of the lumbar nerves L2, 3 and 4 in the lumbar plexus. It emerges under the iliacus fascia at the lateral border of the psoas major to lie in a natural gutter between that muscle and the iliacus (fig. 1). We have seen from our dissections that dye injected into the plane between the muscles of the abdominal trunk, that is the correct plane for infiltration, remains confined to that plane. However, when injected deep to the transversus abdominis the dye tracks towards the femoral nerve under the iliacus fascia which is continuous laterally with the transversalis fascia While this study has demonstrated an anatomical mechanism for spread of local anaesthetic solution if injected in a plane too deep, we can make no definitive comment on the volume of injectate or rate of injection required to result in FNP. It must be noted that spread in the cadaver was achieved using only 1 ml of dye. Even allowing for differences in tissue conditions *in vivo* it seems likely that should sufficient local anaesthetic enter this plane, in the supine position the bony and fascial attachments of the fascial plane inferolaterally (to the ASIS and inguinal ligament) would cause tracking medially and pooling around the femoral nerve with resultant FNP.

An alternative explanation for the observed FNP is that the local anaesthetic is instilled directly around the nerve. Whereas it is not possible to totally discount this mechanism, we have seen from this study that the needle would have to be directed approximately 3–4 cm more medially than is recommended and this would therefore be unlikely. Of interest is the finding of a difference in the distance from the site of injection to the femoral nerve between males and females. The clinical significance of this is that FNP after PIIFB may be less likely to occur in females than males.

Our findings suggest that in a PIIFB for inguinal hernia repair, care should be taken to avoid injecting local anaesthetic deep to the transversus abdominis. This could be achieved by infiltrating the superficial layers, that is the skin and external oblique aponeurosis percutaneously and infiltrating the deeper layers and the ilioinguinal nerve under direct vision after exposure by the surgical incision. Should an entirely percutaneous approach be used, it is essential that the patient is informed of the potential risks, that nursing staff are informed and appropriate precautions are taken to prevent injury resulting from subsequent lower limb weakness.

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# Effects of the pregnant uterus on the extradural venous plexus in the supine and lateral positions, as determined by magnetic resonance imaging

Y. HIRABAYASHI, R. SHIMIZU, H. FUKUDA, K. SAITOH AND T. IGARASHI

## Summary

To clarify the effects of the pregnant uterus on the extradural venous plexus in the supine and lateral positions, we studied magnetic resonance (MR) images of the lumbar spine in three parturients. T2-weighted axial MR images were obtained with the parturient in the supine and lateral positions. On each slice level in the same subject, the MR images were compared with the control MR images obtained before pregnancy. When the parturient lay supine, the pregnant uterus compressed the inferior vena cava and almost totally obstructed it; the extradural venous plexus was engorged. On turning the parturient into the lateral position, the inferior vena cava was free from compression, and the engorged extradural venous plexus was found to shrink to the level of the non-pregnant state. (*Br. J. Anaesth.* 1997; **78**: 317–319)

**Key words**
Anatomy, extradural space. Anaesthesia, obstetric. Measurement techniques, magnetic resonance imaging. Position, supine. Position, lateral. Position, effects.

Obstruction of the inferior vena cava by the pregnant uterus in the supine position diverts a proportion of the return of venous blood from the legs and pelvic structures into the vertebral venous system, causing the extradural venous plexus to engorge.[1] The lateral positioning of the gravida, however, is expected to resolve the vena caval obstruction.[2] Indeed, inferior vena cavogram of the parturient has shown that the lateral position decreases the inferior vena caval obstruction.[1] However, it is not clear if the pregnant uterus in the lateral position affects the extradural venous plexus. Our aim was to compare the lateral position with the supine position for the effects of the pregnant uterus on the extradural venous plexus using magnetic resonance (MR) imaging.

## Methods and results

The Institutional Review Board approved our study and informed consent was obtained. We studied three female volunteers, aged 29–30 yr. T2-weighted axial MR images of the second and third lumbar vertebrae were obtained using an MR imaging system (MRT-200/FXIII super version, Toshiba Corporation, Tokyo, Japan) operating at 1.5 T. Technical specifications included a repetition time of 3000 ms, an echo time of 112 ms, a slice thickness of 4 mm, number of slices 9 and a field of view of 15 cm. Control (non-pregnant) MR images were obtained before pregnancy with the subject in the supine position. At 32–34 weeks' gestation, MR images were obtained with the parturient in the supine position (pregnancy-supine) and the left lateral position (pregnancy-lateral). On each slice level in the same subject, we compared the three images (non-pregnant, pregnancy-supine and pregnancy-lateral). The area of the dural sac at the level of the intervertebral disc between the second and third lumbar vertebrae was measured using a digital planimeter (KP-90N, Uchida Yoko, Ltd, Tokyo, Japan).

Representative MR images are shown in figures 1–3 according to the levels of axial slice. With the parturient supine, the inferior vena cava was almost totally obstructed and the extradural venous plexus was engorged significantly (figs 1B, 2B, 3B). Both the medial and lateral components of the anterior internal vertebral veins were found to expand at the level of pedicles (fig. 1B); lateral components were noted to expand at the levels of the lamina and intervertebral disc (figs 2B, 3B). The engorged anterior internal vertebral veins displaced the anterior dural sac posteriorly (fig. 1B). When the parturient turned to the left lateral position, the inferior vena cava was free from compression and the engorged anterior internal vertebral veins were found to shrink in the lateral position (figs 1C, 2C, 3C). The areas of the dural sac at the level of the intervertebral disc between the second and third lumbar vertebrae (non-pregnant, pregnancy-supine and pregnancy lateral) were 2.0, 1.8 and 2.0 cm$^2$, respectively, in one subject, 1.5, 1.4 and 1.5 cm$^2$ in the second subject, and 1.8, 1.7 and 1.7 cm$^2$ in the third subject.

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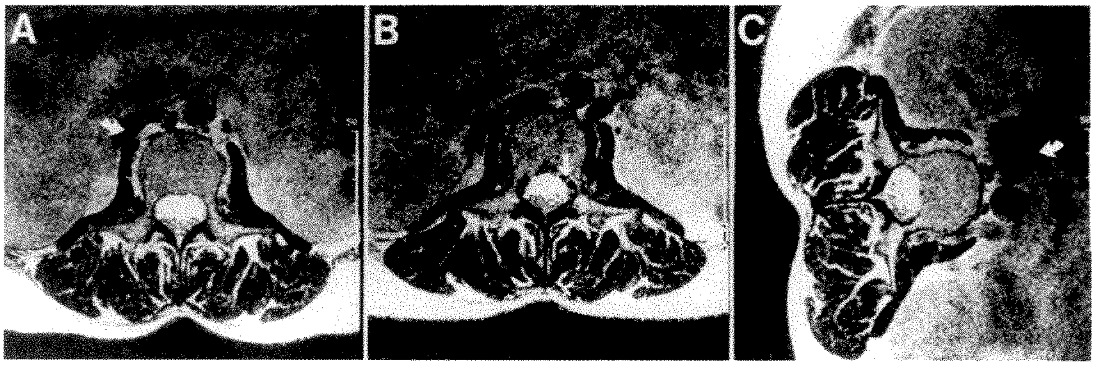

*Figure 1* T2-weighted MR image showing an axial section at the level of the pedicles of L2. A=Non-pregnant, B=pregnancy-supine, C=pregnancy-lateral. The inferior vena cava (curved arrow) was identified in the non-pregnant state (A) and in the pregnant-lateral position (C). Both the medial and lateral components of the anterior internal vertebral veins (vertical arrow) displaced the dura mater locally away from the walls of the vertebral canal (B). When the parturient turned to the left lateral position (C), the inferior vena cava was free from the compression and the engorged anterior internal vertebral veins shrank to the level of the non-pregnant state.

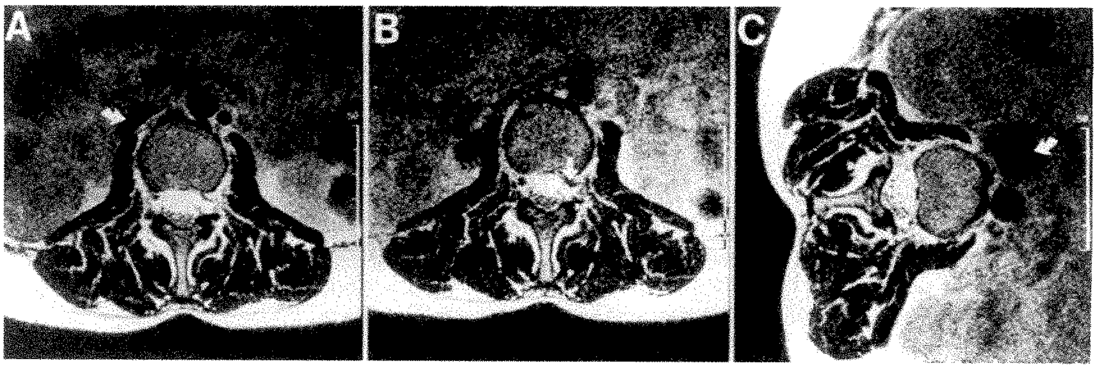

*Figure 2* T2-weighted MR image showing an axial section at the level of the lamina of L2 in the same subject. A=Non-pregnant, B=pregnancy-supine, C=pregnancy-lateral. The inferior vena cava (curved arrow) was identified in the non-pregnant state (A) and in the pregnant-lateral position (C). The lateral components of the anterior internal vertebral veins (vertical arrow) are noted to engorge in the supine position (B), whereas there is no engorgement of the extradural veins in the lateral position (C). The cauda equina was positioned at the posteromedial region of the dural sac in the supine position, while it migrated to the dependent side within the dural sac in the left lateral position.

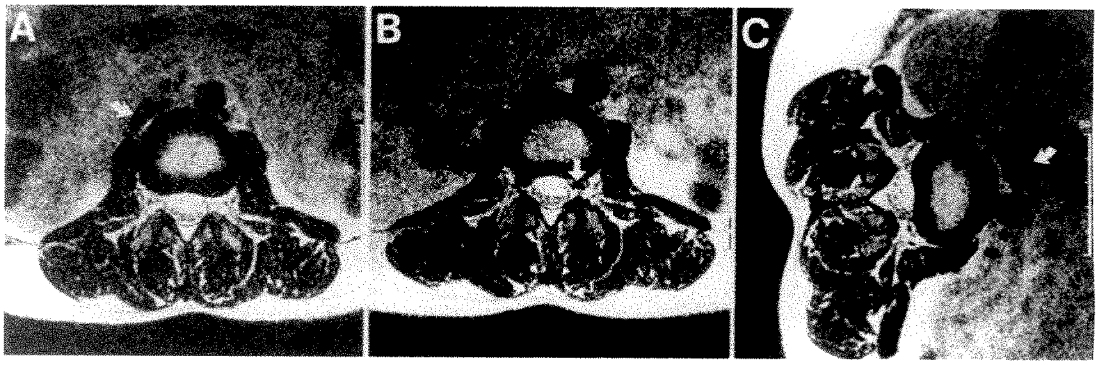

*Figure 3* T2-weighted MR image showing an axial section at the level of the L2–3 intervertebral disc in the same subject. A=Non-pregnant, B=pregnancy-supine, C=pregnancy-lateral. The inferior vena cava (curved arrow) was identified in the non-pregnant state (A) and in the pregnant-lateral position (C). The lateral components of the anterior internal vertebral veins (vertical arrow) are noted to engorge in the supine position (B), whereas there is no engorgement of the extradural veins in the lateral position (C). The fat-filled posterior extradural space remained unchanged at any time.

## Comment

The enlarged uterus in the later stages of pregnancy is expected to affect the return of venous blood from the legs and pelvic structures in two ways: first, the pregnant uterus may directly compress the inferior vena cava in the supine position, and second, it may increase intra-abdominal pressure globally. Of these, direct compression on the inferior vena cava may be resolved by lateral positioning of the gravida.[2] In this study, the inferior vena cava was found to be free from compression when the parturient turned to the left lateral position.

In contrast with direct compression on the inferior vena cava, a global increase in intra-abdominal pressure by the pregnant uterus may affect venous blood flow, regardless of the position. In non-pregnant women, the pressure in the inferior vena cava is normally 4–7 mm Hg in the supine position.[3] This pressure increases to 20–30 mm Hg in late pregnancy. On turning the parturient to the lateral position, the increased pressure was found to decrease rapidly to approximately 10–15 mm Hg.[4] This moderate pressure increase in the inferior vena cava in the lateral position may result from a global increase in intra-abdominal pressure by the enlarged pregnant uterus. In our parturients in the supine position, the anterior internal vertebral veins were found to engorge significantly. This engorgement of the anterior internal vertebral veins may result from diversion of the return of venous blood from the legs and pelvic structures to the vertebral venous system, which is induced by direct compression on the inferior vena cava in the supine position. On turning the parturient to the lateral position, the engorged anterior internal vertebral veins were found to shrink to the level of the non-pregnant state. This suggests that, with respect to the lateral position, the pregnant uterus may not divert the return of venous blood from the legs and pelvic structures to the vertebral venous system. It is unlikely that, in the lateral position, a global and moderate increase in intra-abdominal pressure associated with the pregnant uterus alone causes the extradural veins to engorge. The enlarged uterus during the later stages of pregnancy may cause the extradural venous plexus to engorge mostly by direct compression on the inferior vena cava rather than a global and moderate increase in intra-abdominal pressure.

Recently, Hogan and colleagues[5] investigated the effects of abdominal compression on CSF volume using MR imaging. The authors reported that abdominal compression decreased CSF volume, and that the mechanism by which increased abdominal pressure decreases CSF volume is probably inward movement of soft tissue in the intervertebral foramen, which displaces CSF. Unlike their study, we failed to demonstrate inward movement of soft tissue in the intervertebral foramen, while the engorged extradural venous plexus displaced the dural sac. Our findings are not directly comparable with theirs because both subjects and methods differed between the two studies. In addition, it is likely that the mechanism by which CSF volume is decreased in the parturient may differ from that in brief abdominal compression.

Although we showed that the inferior vena cava became free from compression and the engorged anterior internal vertebral veins shrank during the lateral position, the number of subjects studied was so small that the findings cannot be simply applied to the population as a whole. The availability of pre-pregnant controls, however, provided persuasive findings on the influence of the supine and lateral positions in determining extradural compliance and the volume of the dural sac at the level of the lumbar spine. It would be necessary to study a substantially larger population to confirm these findings and their relation to the spread of regional anaesthesia.

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# Effect of lipid and propofol on oxidation of haemoglobin by reactive oxygen species†

N. STRATFORD AND P. MURPHY

## Summary

The clinical formulation of the i.v. anaesthetic propofol contains both the substrate for and inhibitor of lipid peroxidation. In these *in vitro* experiments we have investigated the importance of this potential conflict in a system where haemoglobin was oxidized by reactive oxygen species generated by hypoxanthine and xanthine oxidase. The presence of lipid in the system accelerated the rate of haemoglobin oxidation. Propofol inhibited lipid-induced acceleration but not the underlying rate of reactive oxygen species-induced oxidation. The rate of conjugated diene production, measured semi-quantitatively by ultraviolet absorption at 234 nm, was not reduced by propofol. Propofol may act by preventing haemoglobin oxidation by lipid hydroperoxides. (*Br. J. Anaesth.* 1997; **78**: 320–322)

**Key words**
Anaesthetics i.v., propofol. Blood, haemoglobin. Metabolism, lipids. Formulations, propofol.

Lipid peroxidation is a consequence of radical generation in biological tissues and may contribute to the tissue injury induced by oxidant stress. Propofol (2,6-diisopropylphenol) is an established inhibitor of radical-induced lipid peroxidation.[1 2] However, in its clinical formulation as Diprivan, this agent is dissolved in an emulsion of egg phosphatide, soya bean oil and glycerol, an emulsion vehicle similar to the i.v. feeding solution Intralipid. Diprivan therefore presents both substrate for and inhibitor of lipid peroxidation.

In these *in vitro* experiments we have considered the importance of this potential conflict by investigating the effect of propofol and lipid on a radical-mediated process—oxidation of ferrous haemoglobin by reactive oxygen species generated by a xanthine oxidase–hypoxanthine system. Haemoglobin is an attractive target as it is susceptible to easily measured oxidant-induced changes initiated by both reactive oxygen species and products of lipid peroxidation.[3] We speculated that lipid peroxidation might take place when reactive oxygen species (ROS) are generated in the presence of Diprivan or Intralipid. Therefore, in separate experiments, we followed the extent of this process by measuring the concentration of conjugated dienes, intermediate products of lipid peroxidation.

## Methods and results

Commercial human haemoglobin, largely methaemoglobin, was converted to the ferrous state by reduction with excess dithionite and purified by Sephadex gel separation. Solutions of oxyhaemoglobin 50 μmol litre$^{-1}$ in phosphate-buffered saline (pH 7.4) were incubated with a ROS generating system consisting of xanthine oxidase 0.01 u. ml$^{-1}$ and hypoxanthine 0.5 mmol litre$^{-1}$ at 37 °C for 4 h (all reagents from Sigma). Light absorbance at 560, 577 and 630 nm was measured spectrophotometrically (Pye Unicam PU 8600 UV/VIS) at the beginning of each experiment and after 2 and 4 h. The concentration of oxyhaemoglobin was calculated using equations derived from the known absorption coefficients of haemoglobin at each wavelength[3]:

$$[\text{oxyhaemoglobin}] = 0.0684A_{577} - 0.0014A_{560} - 0.0822A_{630}$$

where A=measured absorbance at each wavelength after correction for background absorbance measured at 700 nm. After 4 h, total haemoglobin concentration in our experiments decreased abruptly, making interpretation of oxidative changes impossible. The effect of including 0.005%, 0.01% and 0.02% Intralipid (Pharmacia) or propofol 25, 50 and 100 μmol litre$^{-1}$ as Diprivan (Zeneca) in the reaction flasks was examined. Concentrations of Intralipid provided an equivalent of the concentration of lipid accompanying each concentration of propofol formulated as Diprivan.

The amount of lipid peroxidation in the presence of either Intralipid or Diprivan was measured in a semi-quantitative manner by repeating the experiments in the absence of haemoglobin and measuring ultraviolet absorption at 234 nm. This provides a non-specific measure of conjugated dienes, a major product of polyunsaturated lipid peroxidation.

All experiments were performed six times and

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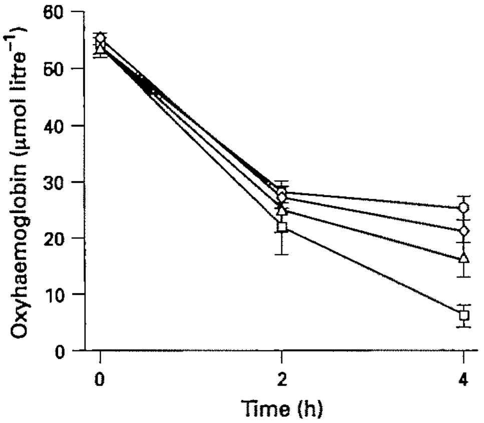

*Figure 1* Oxyhaemoglobin concentrations (mean, 95% confidence intervals) in experiments containing lipid. ○=Saline control, □=0.02% lipid, △=0.01% lipid, ◇=0.005% lipid.

results are expressed as mean (95% confidence intervals). Where there were differences, results were compared using two-way analysis of variance (ANOVA).

In the haemoglobin experiments there was a decrease in the concentration of oxyhaemoglobin over 4 h, consistent with ROS-mediated oxidation from the ferrous to the met-state. Haemoglobin oxidation was faster in flasks containing Intralipid than in saline control flasks (fig. 1). This effect was dependent on the concentration of lipid (two-way ANOVA, $P<0.001$). There was no difference in the rate of haemoglobin oxidation between Diprivan and saline control experiments.

In the haemoglobin-free experiments, absorbance at 234 nm increased steadily from 0 to 0.398 (95% confidence intervals 0.362–0.434) absorption units after 4 h in the Intralipid experiments and from 0 to 0.409 (0.373–0.445) absorption units over the same period in the Diprivan experiments. That there was no difference indicates that the formation of conjugated dienes occurred at the same rate in both Intralipid and Diprivan experiments.

## Comment

Xanthine oxidase catalyses the oxidation of hypoxanthine to xanthine with the consequent one electron reduction of molecular oxygen to the radical superoxide anion ($O_2^{\cdot-}$). Superoxide anions spontaneously dismute to produce hydrogen peroxide ($H_2O_2$). When exposed to this system, oxyhaemoglobin ($Hb\text{-}Fe^{2+}\text{-}O_2$) is oxidized to higher oxidation states such as met- ($Hb\text{-}Fe^{3+}$) and ferryl- ($Hb\text{-}Fe^{4+}$) haemoglobin.[4]

In these experiments we have shown that Intralipid potentiated the oxidation of oxyhaemoglobin by the xanthine oxidase–hypoxanthine system in a concentration-dependent manner. In contrast, the effect of propofol was more complex. It had no effect *per se* on oxidation of haemoglobin. However, because samples to which Diprivan was added did not exhibit the accelerated rates of oxidation observed in the Intralipid experiments, it is implied that propofol inhibited the effect of lipid. Thus propofol appeared to prevent lipid-induced acceleration of haemoglobin oxidation but did not reduce the underlying ROS-induced oxidation.

The mechanism underlying these observations is not clear. The increase in conjugated diene concentration during the course of the experiments is clear evidence of lipid peroxidation taking place when either Diprivan or Intralipid are exposed to this oxidant system. The process of lipid peroxidation is a self-propagating one which produces lipid hydroperoxides (LOOH) as end products. These species are themselves capable of oxidizing oxyhaemoglobin in a manner similar to the simplest hydroperoxide, hydrogen peroxide (HOOH). We hypothesize that the higher rate of haemoglobin oxidation observed in the presence of Intralipid is because of formation of lipid hydroperoxides.

The explanation for the activity of Diprivan is more complicated. Our experiments suggest that propofol within the formulation inhibits the effect of lipid on haemoglobin oxidation. There are several possible mechanisms for this. Propofol (P-OH) is a known inhibitor of lipid peroxidation.[1 2] It terminates the chain reaction of lipid peroxidation by reacting with lipid radicals forming a relatively stable phenoxyl radical ($PO^{\cdot}$).[5] However, failure of propofol to reduce the level of conjugated dienes formed during our experiments suggests that this is not the case in this system. Alternative explanations are that propofol either prevents the oxidation of haemoglobin by lipid hydroperoxides or that it reduces met-haemoglobin formed during the oxidative process back to the ferrous state. While there is evidence that the latter process can occur,[3] prevention of haemoglobin oxidation by lipid hydroperoxides is the most appealing explanation for our observations.

Failure to demonstrate a lower degree of lipid peroxidation in Diprivan compared with Intralipid experiments requires further comment. Other workers have shown that propofol at concentrations equivalent to or lower than those used here inhibit lipid peroxidation in liver microsome[1 6] and plasma models.[5] In some of these models the antioxidant activity of propofol was dependent on a supply of reduced glutathione, presumably to recycle the propofol phenoxyl radical species back to the reduced state.[2] No such system was available in our model. Furthermore, in our experiments the relative excess of lipid substrate may imply that any inhibitory effect on lipid peroxidation of the available propofol is simply swamped. Nevertheless, this is a relevant investigation as this is the formulation in which the drug is administered to patients for both anaesthesia and sedation in the intensive therapy unit.

The clinical implications of this study are not clear, but suggest that further investigation is required. The systemic inflammation exhibited by many critically ill patients in response to infection or trauma exposes them to an oxidant stress which is believed to contribute to subsequent tissue injury and secondary organ dysfunction. Further, lipid-containing solutions are often administered to this group of patients, either as part of a parenteral nutrition regimen or in the form of Diprivan to provide sedation. While it is not known if administration of lipid under such circumstances adds to a patient's oxidative stress, such a hypothesis would be worthy of examination. It is tempting to speculate that propofol could be a clinically useful antioxidant. However, both this work and that of Aarts and colleagues[2] have shown that, with regard to lipid peroxidation at least, simply giving a single antioxidant compound may not be the whole answer.

## Acknowledgements

We are grateful to Sheila Radford for technical assistance and to Dr Colin Bolton, Bristol University Department of Medicine, for advice.

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# Validation of thoracic electrical bioimpedance as a porcine research tool

C. J. BROOMHEAD, S. J. WRIGHT, K. M. KIFF AND P. S. WITHINGTON

## Summary

We have compared the accuracy of two methods of measuring cardiac output, thoracic electrical bioimpedance (TEB) and thermodilution (TD), in pigs. We studied four anaesthetized pigs, producing 145 paired cardiac output values over a range of TD cardiac outputs of 2.6–12.6 litre $\text{min}^{-1}$. TEB cardiac output was less than that measured by TD, by a constant factor throughout the observed range of values, because of differences in porcine thoracic shape. The Pearson product moment correlation coefficient suggested a good correlation ($r$=0.984, $P$<0.001). More importantly, analysis by the Bland and Altman statistical method suggested a high level of agreement, with 95% confidence intervals of ±1.0 litre $\text{min}^{-1}$. These results suggest that TEB can be used as a satisfactory method to measure cardiac output in porcine models. (*Br. J. Anaesth.* 1997; **78**: 323–325).

**Key words**
Measurement techniques, cardiac output. Measurement techniques, thoracic electrical bioimpedance. Measurement techniques, thermodilution. Pig.

Thermodilution is the most commonly used method of determining cardiac output. However, disadvantages associated with this technique, not least those caused by insertion of pulmonary artery catheters, are exaggerated in animal based research because of lack of familiarity with the anatomy. In contrast, thoracic electrical bioimpedance (TEB) is quick and simple to use, has minimal risks and provides continuous data. TEB has been used in humans, from neonates to adults, from the critically ill to the pregnant. Only one study has investigated its use in animals[1] and this can be criticized on the basis of statistical analysis as only a correlation coefficient was calculated. We have investigated the accuracy of TEB in a porcine model to assess its value as a research tool.

## Methods and results

We studied four unpremedicated large white pigs, weighing 40–50 kg. After induction of anaesthesia by inhalation of 5% halothane, and nitrous oxide in oxygen in a 50:50 mixture, the trachea was intubated and the lungs ventilated with a Cape-Waine ventilator and circle system. Anaesthesia was maintained with 2% halothane in a mixture of nitrous oxide in oxygen. Before surgery, continuous thoracic bioimpedance cardiac output monitoring was commenced (BoMed NCCOM3-R7 Continuous Cardiodynamic Monitor, Kimal Electronics Ltd, Cheshire, UK, using the software revision 7). Self-adhesive electrode pads, with two electrodes exactly 5 cm apart, were supplied by the manufacturers. Four pairs of electrodes are required, placed symmetrically on the thorax, at the base of the neck and in the midaxillary line at the level of the xiphoid process. An extra pair of electrodes placed over the cardiac apex ensures accurate monitoring of the ECG. Weight, height (snout to rump) and sex variables were entered, and cardiac output, averaged over 10 s, allowed stable data production.

Midline laparotomy allowed insertion of a Swan–Ganz catheter via the inferior vena cave and cannulation of the abdominal aorta. Cardiac output was measured by TD (Baxter EF1) using the mean of triplicate injections of 10 ml of iced 5% glucose injected as fast as possible at end-expiration. Repeated paired measurements of cardiac output by TD and TEB were performed every 10 min for 120 min. After this period, adrenaline infusions and progressive exsanguination were used to further extend the range of cardiac outputs over which measurements were obtained.

A total of 145 paired data points were collected over a range of TD cardiac output values from 1.7 to 8.6 litre $\text{min}^{-1}$. Differences in the shape of the porcine and human thorax generates a constant error in estimated cardiac output. Although TD cardiac output values were greater than TEB over the whole range of outputs measured, by multiplying TEB cardiac output values by a correction factor of 1.48, this error was eliminated.

The Pearson product moment correlation coefficient was $r$=0.984 with $P$<0.001. Data were also

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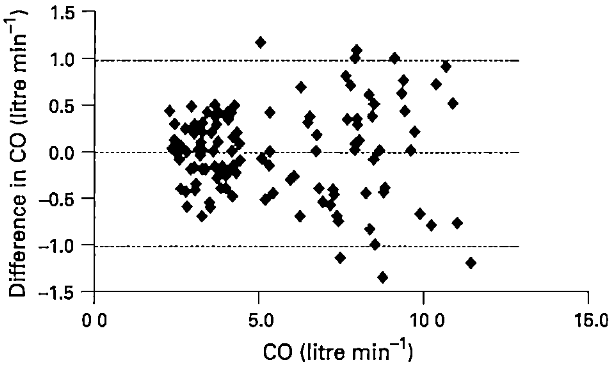

*Figure 1* Mean of simultaneous thermodilution and bioimpedance cardiac output (CO) values *vs* the difference between them. Mean difference (0.01 litre min$^{-1}$) and the limits of agreement (upper 1.01 litre min$^{-1}$, lower −0.99 litre min$^{-1}$) are shown as horizontal lines.

analysed according to the method described by Bland and Altman.[2] A plot of the differences between cardiac output measurements against the mean of the two measurements (fig. 1) showed no relationship between the measurement error and the true value (i.e. no consistent bias). The mean of the differences was 0.01 (SD 0.51) litre min$^{-1}$ and there was a Gaussian distribution of values. Therefore, 95% confidence interval of the differences was +1.01 (upper limit) to −0.99 (lower limit) litre min$^{-1}$ (SD 1.96); SEM was 0.042 litre min$^{-1}$. The precision of these estimated (mean, upper and lower) limits of agreement was derived using a $t$ test with 144 ($n-1$) degrees of freedom and calculating 95% confidence intervals for each of the limits. Thus the mean was 0.01 (SEM 0.08) litre min$^{-1}$. The 95% confidence interval for the other limits was similarly ±0.08 litre min$^{-1}$.

## Discussion

If an alternating current of constant magnitude is passed across the thorax, changes in impedance are related to variations in aortic blood flow, as air in the lungs, fat in the subcutaneous tissue and ribs traversing the muscles minimize conductance of these tissues. The outer four electrodes produce a constant high frequency current longitudinally across the thorax, generating a high frequency voltage in the same direction, which is proportional to the TEB. The inner electrodes sense changes in this voltage and the ECG, enabling changes in thoracic blood volume to be related to the cardiac cycle. The rate of change of impedance is used to calculate stroke volume, and from heart rate (detected by the ECG), cardiac output can be derived.[3]

The NCCOM3-R7 is simple to use. Four paired electrode pads are applied symmetrically to the chest, two at the base of the neck and the two in the middle of the sixth rib at the level of the xiphoid process. Careful positioning is needed as small changes in distance between cervical and thoracic electrodes may produce significant changes in stroke volume estimates. Beat-to-beat generation of data is possible, but makes assessment of changes and trends difficult; an averaging time of 10 s is more useful. ECG detection is the only difficulty we encountered using the NCCOM3-R7 and this was overcome using the extra pair of sensing electrodes supplied. As in humans, heart rates of greater than 175 beat min$^{-1}$ and arrhythmias were difficult for the NCCOM3-R7 to follow.

In studies comparing two methods of measurement, a Pearson product moment correlation coefficient is frequently quoted with a probability, as in the article of Spinale, Reines and Crawford ($r$=0.91 and $P$<0.001).[1] Despite the apparently impressive correlation, this is a poor analysis of two methods of measurement[2]: $r$ measures the strength of a relationship between two variables rather than agreement between them. Further, the strength of the correlation depends on the range over which cardiac output is measured and increases as the range increases. Most studies compare two methods over a large range of values (as we have done), almost guaranteeing a high correlation coefficient.

A simple and accurate alternative analysis, which is accepted widely as being more appropriate for such comparative studies, has been offered by Bland and Altman[2] and has been applied to our data. The mean of the measured cardiac outputs is plotted against the difference between these values (fig. 1). The mean of the differences can be calculated (in this case 0.01 litre min$^{-1}$), as can the SD (0.51 litre min$^{-1}$). The limits of agreement for TEB and TD were therefore ±1.0 litre min$^{-1}$ (95% confidence interval is calculated as mean ±1.96×SD). The precision of these estimates was determined using a $t$ test and the SEM to calculated 95% confidence interval as ±0.08 litre min$^{-1}$ (±1.96×SEM). There are two components to this error: within-technique and between-technique variability. TEB, unlike TD, is known to have a low within-technique variability (high level of repeatability),[4] perhaps because it averages a number of consecutive stroke volumes.[4] The between-technique variability should approach the within-technique variability for TD, that is <1 litre min$^{-1}$. Our data fell within this range and certainly the between-technique variability was far less than the within-technique repeatability reported by some groups for TD.[5] In the few studies using Bland and Altman statistics in humans, the quoted bias varied from −0.15 (SD 0.86)[6] to −0.7 (1.7).[4] Our results of 0.01 (0.51) compare favourably with these values. We can conclude that there is a high level of agreement between TEB and TD when allowance is made for the difference in chest geometry between the pig and humans, and that the variation is acceptably small.

## Acknowledgements

This work was supported by a grant from the Intensive Care Society and by the Elizabeth Wherry award from the British Medical Association.

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# Effects on haemodynamics and catecholamine release of xenon anaesthesia compared with total i.v. anaesthesia in the pig

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## Summary

In order to investigate haemodynamic response and catecholamine release during anaesthesia with xenon, we conducted a study on 28 pigs which were allocated randomly to one of four groups: total i.v. anaesthesia with pentobarbitone and buprenorphine, and xenon anaesthesia with inspiratory concentrations of 30%, 50% or 70%, respectively, supplemented with pentobarbitone. Haemodynamic variables were measured using arterial and Swan Ganz catheters. Depth of anaesthesia was monitored using spectral edge frequency analysis. Plasma concentrations of dopamine, noradrenaline and adrenaline were measured by high pressure liquid chromatography. All haemodynamic variables and plasma concentrations of dopamine and noradrenaline remained within normal limits. Adrenaline concentrations were reduced significantly in all groups. Xenon anaesthesia was associated with a high degree of cardiovascular stability. Significant reduction in adrenaline concentrations at inspiratory xenon concentrations of 30% and 50% can be explained by analgesic effects of xenon below its MAC value. (*Br. J. Anaesth.* 1997; **78**: 326–327)

**Key words**
Anaesthetics volatile, xenon. Sympathetic nervous system, catecholamines. Cardiovascular system, effects. Pig.

To investigate dose-dependent influences of xenon anaesthesia on haemodynamic variables and catecholamine release, we studied different concentrations of xenon in an animal experiment.

In a study performed with 70% xenon supplemented by fentanyl, heart beat frequencies (HBF), arterial pressure and plasma catecholamine concentrations were measured, and the data compared with values obtained during nitrous oxide anaesthesia. Increases in noradrenaline concentrations, decreases in plasma adrenaline concentrations and a tendency for the HBF to decrease were seen. The cumulative dose of fentanyl was reduced by 80% in the xenon group.[1 2] Cardiac contractility, monitored by transoesophageal echocardiography, was not influenced by xenon anaesthesia.[3]

## Methods and results

We studied 28 pigs, aged 12–16 weeks, weighing 34.5–42.9 kg which were allocated randomly to one of four groups: group 1, total i.v. anaesthesia; group 2, anaesthesia with inspiratory xenon concentrations of 30%; group 3, 50% xenon; group 4, 70% xenon. Anaesthesia was induced with a bolus dose of pentobarbitone 8 mg $kg^{-1}$ and buprenorphine 0.01 mg $kg^{-1}$ i.v. Neuromuscular block was produced with a single dose of alcuronium 0.25 mg $kg^{-1}$. Anaesthesia was maintained with a constant infusion of pentobarbitone 0.2 mg $kg^{-1}$ $min^{-1}$. The rate of infusion was adjusted to the level of anaesthesia. Depth of anaesthesia was assessed using a spectral edge frequency SEF95 monitor. Intermittent positive pressure ventilation was carried out using a partial rebreathing system and ventilation volume was adjusted to achieve normocapnia. Inspiratory and expiratory xenon concentrations were measured by mass spectrometry .

A Swan-Ganz catheter was placed via the right internal jugular vein and a cannula was inserted into the right femoral artery. After these procedures the animals were left unstimulated for 60 min. The femoral artery was then dissected by open surgery under anaesthesia according to the randomization. At the request of the Animal Care Commission, animals in the TIVA group received an additional analgesic dose of buprenorphine 0.01 mg $\cdot kg^{-1}$ before skin incision. In the xenon groups, no additional analgesia was given. Serum concentrations of adrenaline, noradrenaline and dopamine were measured using high pressure liquid chromatography (HPLC) (table 1). The detection limit of each catecholamine was 2 pg $ml^{-1}$; accuracy was 3.9% for noradrenaline, 5.2% for adrenaline and 5.0% for dopamine.

## Comment

We observed a significant reduction in plasma adrenaline concentrations during xenon anaesthesia, not only at inspiratory concentrations of approximately 1 MAC, but even at subanaesthetic concentrations of 30% and 50%. Because all animals in the xenon groups received significantly less pentobarbitone than

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*Table 1* Haemodynamic variables (cardiac index, mean arterial pressure, systemic vascular resistance (SVR), pulmonary vascular resistance (PVR)), plasma catecholamine concentrations and dose of additional i.v. pentobarbitone (median (25th–75th percentiles). *$P<0.05$ compared with control

| | Group | | | | |
|---|---|---|---|---|---|
| | Control | TIVA | Xenon 30 % | Xenon 50% | Xenon 70% |
| Cardiac index | 4.90 | 4.92 | 4.79 | 4.31 | 4.46 |
| (litre min$^{-1}$ m$^{2}$) | (4.51–5.60) | (4.23–5.31) | (4.41–5.0) | (4.05–4.65) | (4.29–4.83) |
| Mean arterial pressure | 105.0 | 96.0 | 104.0 | 109.50 | 110.0 |
| (mm Hg) | (96.0–110.0) | (87.0–103.0) | (97.0–109.0) | (107.0–115.0) | (98.0–114.0) |
| Mean pulmonary pressure | 19.0 | 17.0 | 20.0 | 20.50 | 21.0 |
| (mm Hg) | (15.75–21.25) | (15.0–19.0) | (18.0–21.0) | (18.0–22.0) | (19.0–22.0) |
| SVR | 1366.5 | 1419.0 | 1463.0 | 1486.5 | 1475.0 |
| (dyn s cm$^{-5}$) | (1175.0–1560.0) | (1175.75–1561.25) | (1273.25–1517.0) | (1327.0–1653.0) | (1423.25–1790.75) |
| PVR | 188.0 | 186.0 | 176.0 | 210.0 | 220.5 |
| (dyn s cm$^{-5}$) | (159.0–224.5) | (154.75–220.0) | (161.25–189.0) | (179.25–243.0) | (208.0–238.0) |
| Adrenaline | 84.0 | 15.0* | 39.0* | 17.0* | 15.0* |
| (pg ml$^{-1}$) | (40.8–223.0) | (15.0–46.8) | (15.5–53.0) | (15.0–32.5) | (15.0–48.0) |
| Dopamine | 73.5 | 130.5 | 85.0 | 63.5 | 77.0 |
| (pg ml$^{-1}$) | (49.5–126.0) | (86.5–177.0) | (53.0–131.0) | (47.5–110.5) | (45.5–112.5) |
| Noradrenaline | 48.0 | 40.0 | 52.5 | 30.0* | 42.5 |
| (pg ml$^{-1}$) | (31.0–76.0) | (30.8–71.3) | (36.5–66.0) | (21.5–47.0) | (29.0–62 0) |
| Infusion rate of pentobarbitone | 0.470 | 0.234* | 0.12* | 0.092* | 0.093* |
| (mg kg$^{-1}$ min$^{-1}$) | (0.38–0.48) | (0.22–0.24) | (0.11–0.17) | (0.07–0.10) | (0 06–0.12) |

those in the TIVA group, although no additional buprenorphine was given, the decrease in adrenaline concentrations in the xenon groups may have been produced by the analgesic effects of xenon, even in concentrations below its MAC value.[4]

All haemodynamic variables were not influenced by xenon anaesthesia and remained at normal values for conscious pigs and during anaesthesia. Because infusion rates of pentobarbitone of up to 0.6 mg kg$^{-1}$ min$^{-1}$ are known not to influence mean arterial pressure and cardiac output,[5] the influence of additional pentobarbitone infusion on haemodynamic values may be regarded as unimportant in our study. Therefore, we found that xenon was an inhalation anaesthetic with little influence on the cardiovascular system. This may represent an important difference to other inhalation anaesthetics.[6]

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# Pregnenolone sulphate and pregnenolone do not interact with 5β-pregnanolone- and hexobarbitone-induced anaesthesia in the rat

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## Summary

We have studied the interaction of pregnenolone sulphate and pregnenolone with 5β-pregnanolone- and hexobarbitone-induced anaesthesia in male rats using an EEG threshold method. Burst suppression of the EEG of 1 s or more ("silent second" (SS)), was used as a criterion of deep anaesthesia. The effects of the steroid solvents albumin and β-cyclodextrin were assessed by dose–response curves. Despite a significant increase in hexobarbitone threshold dose in relation to increased doses of albumin, there was no correlation between albumin dose and hexobarbitone concentrations in serum, fat and brain tissues. There was no significant difference in threshold concentrations of hexobarbitone between controls given albumin and those pretreated with pregnenolone. In subsequent experiments, 20% β-cyclodextrin was used as steroid solvent and its volume was maintained at less than 3.0 ml $kg^{-1}$ during pretreatment. Neither pregnenolone sulphate nor pregnenolone significantly altered the potency of 5β-pregnanolone for induction of anaesthesia. Furthermore, there was no interaction of pregnenolone sulphate and pregnenolone on induction of anaesthesia when hexobarbitone was used for anaesthesia. (*Br. J. Anaesth.* 1997; **78**: 328–331).

**Key words**
Anaesthetics i.v., pregnanolone. Anaesthetics i.v., hexobarbitone. Rat. Hormones, steroid.

The synthesis of steroid hormones in endocrine tissues begins with cholesterol side chain cleavage (P450scc) which converts cholesterol to pregnenolone (5-pregnen-3β-ol-20-one). 3β-Hydroxysteroid dehydrogenase/isomerase converts pregnenolone to progesterone. Progesterone metabolites that are reduced in the 5-position of the steroid molecule are very potent CNS depressants, particularly those with a 3α-hydroxy-20-ketone structure. 5β-Pregnanolone (3α-hydroxy-5β-pregnan-20-one) is a naturally occurring anaesthetic which accumulates in the brain and interacts with central $GABA_A$ receptors as agonist.[1] Pregnenolone and its sulphate ester pregnenolone sulphate have been shown to be synthesized in glial cells in the brain via side chain cleavage of cholesterol. Brain concentrations appear to be independent of gonadal and adrenal synthesis.[1] Electrophysiological studies revealed that pregnenolone sulphate interacts with the $GABA_A$ receptor as antagonist.[1] *In vivo*, Majewska and coworkers[2] found that pregnenolone sulphate antagonized barbiturate-induced anaesthesia in rats, while Melchior and Allen[3] observed that pregnenolone sulphate enhanced barbiturate-induced depression in motor activity without affecting anaesthesia. The aim of this study was to evaluate the interaction of pregnenolone and pregnenolone sulphate with 5β-pregnanolone- and hexobarbitone-induced anaesthesia. In addition, we investigated the effects of the solvents albumin and β-cyclodextrin on induction of anaesthesia.

## Methods and results

A previously described EEG threshold method (see Korkmaz, Ljungblad and Wahlström[4] for references) was used to induce anaesthesia with hexobarbitone and 5β-pregnanolone. Anaesthetics were infused into the tail vein at a constant dose rate. The EEG was monitored continuously via subcutaneous electrodes. The infusion was terminated when the first burst of EEG suppression for 1 s or more was noted (the "silent second", SS). The appearance of SS occurs at a deeper level of anaesthesia than loss of righting reflex. The amount of anaesthetic needed to induce SS was calculated and considered as the threshold dose. A dose rate curve was generated by repeated measurements of threshold doses with different dose rates. The dose rate which gave the lowest threshold dose at SS was defined as the optimal dose rate. Data are expressed as mean (SD) and software SPSS was applied for data analysis.

After obtaining Ethics Committee approval a preliminary study was carried out to examine the effect of the solvent, albumin, on hexobarbitone-induced anaesthesia. Thirty-five male, adult Sprague–Dawley rats (MOL:SPDR Möllegaard, Ll. Skensved, Denmark) (mean weight 574 (45) g, aged 300–310 days) were used and pregnenolone (Sigma, MI,

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USA) was dissolved in human albumin (Novo Nordisk, Bagsvard, Denmark, 20 mg $ml^{-1}$) at a concentration of 0.7 mg $ml^{-1}$. Sodium hexobarbitone (Sigma, MI, USA) was prepared in 0.9% saline and infused at an optimal dose rate of 15 mg $kg^{-1}$ $min^{-1}$ established previously. The volume rate was 0.1 ml $min^{-1}$ (see Korkmaz, Ljungblad and Wahlström[4] for references). Fifteen minutes before infusion of hexobarbitone, rats were pretreated with pregnenolone 3.5–7.0 mg $kg^{-1}$ i.v. As a control, the albumin solution was used to pretreat rats at equivalent volumes. The infusion volume rate for pretreatment was 1 ml $min^{-1}$.

A significant increase in hexobarbitone threshold dose was observed from 54.0 (8.4) mg $kg^{-1}$ in untreated rats to 108.6 (19.4) mg $kg^{-1}$ for the highest dose of pregnenolone pretreatment ($F_{2,18}$= 7.03, $P<0.05$). An increase in hexobarbitone threshold from 54.0 (8.4) mg $kg^{-1}$ in untreated rats to 103.4 (12.8) mg $kg^{-1}$ in rats given the highest volume of albumin was also found in albumin controls ($F_{2,19}$=22.86, $P<0.05$). Two-way ANOVA revealed no significant difference in threshold doses of hexobarbitone between pregnenolone pretreated rats and controls ($F_{2,19}$=0.05, $P$=0.96). The rats were killed at SS and hexobarbitone concentrations in serum, fat, occipital cortex, cerebellum, mid-brain and medulla oblongata were measured by HPLC and UV spectrophotometry, essentially according to a method described in detail previously.[4] Although there was a significant increase in hexobarbitone threshold doses in relation to increased dose of albumin, there was no significant correlation between albumin dose and hexobarbitone concentrations in serum, fat and brain tissues for either controls or pregnenolone pretreated rats (fig. 1). Furthermore, there was no significant difference in hexobarbitone concentrations in any tissue between controls and pregnenolone pretreated rats ($F_{3,85}$=1.71, $P$=0.17, two-way ANOVA).

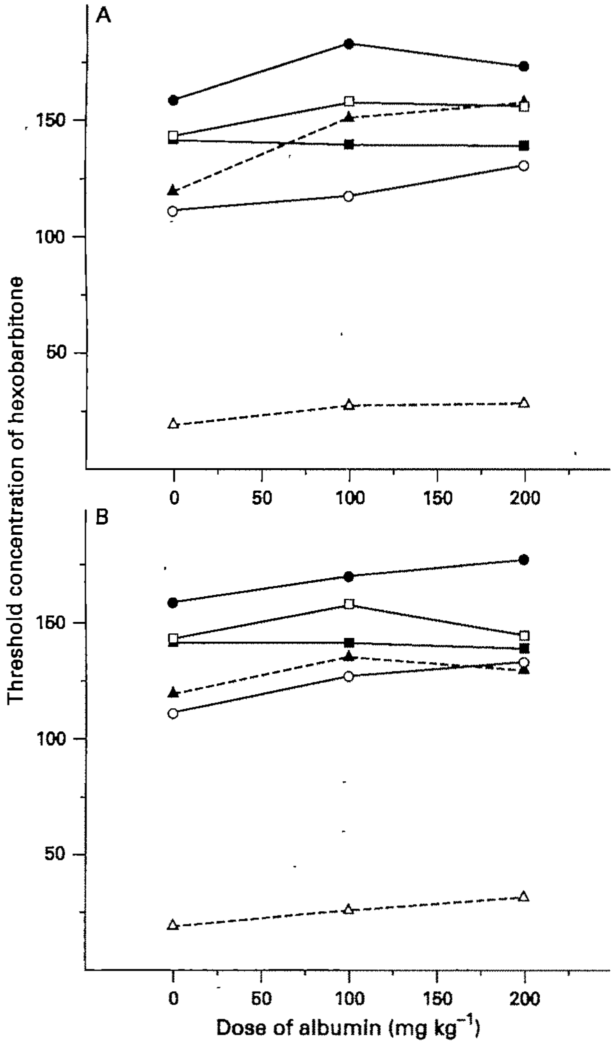

*Figure 1* Relationship between threshold concentrations of hexobarbitone at silent second (serum μg $ml^{-1}$, fat and brain tissue μg $g^{-1}$) and dose of albumin in vehicle controls given albumin (A) and rats pretreated with pregnenolone (B). ▲=Serum; △=fat; ●=medulla oblongata; ○=midbrain; ■=occipital cortex; □=cerebellum.

We used 130 male rats (mean weight 328 (12) g, aged 65–70 days) to examine the interaction of pregnenolone and pregnenolone sulphate (Sigma, MI, USA) with 5β-pregnanolone- (CoCensys, Inc., Irvine, CA, USA) induced anaesthesia. Pregnenolone 5.0 mg $ml^{-1}$, pregnenolone sulphate 6.0 mg $ml^{-1}$ and 5β-pregnanolone 4.0 mg $ml^{-1}$ were dissolved in 20% β-cyclodextrin (Sigma, MI, USA) (β-cyclodextrin 2.0 g in 10 ml of distilled water) in 15-ml aliquots. They were placed in the Bransonic 2210 ultrasonic bath for 15 h and agitated occasionally. After exposure to sonication, all steroids were wetted by visual inspection. Cyclodextrins are cyclic oligosaccharides consisting of 6–8 glucose units which can form inclusion compounds with guest molecules and thereby improve drug solubility and bioavailability.

The relationship between threshold doses of 5β-pregnanolone at SS and dose rate used for infusion of 5β-pregnanolone was determined ($n$=14). The volume rate of the 5β-pregnanolone infusion was 0.35 ml $min^{-1}$. Three dose rates (2.0, 3.0, 4.0 mg $kg^{-1}$ $min^{-1}$ ) were tested. A dose rate of 3.0 mg $kg^{-1}$ $min^{-1}$ was defined as the optimal dose rate. In a control experiment, rats were pretreated with 20% β-cyclodextrin i.v. at volumes of 3.0, 6.0 and 12.0 ml $kg^{-1}$, 15 min before infusion of 5β-pregnanolone ($n$=25). A significant increase in 5β-pregnanolone threshold doses was observed at SS which was related to the volume of β-cyclodextrin ($F_{3,24}$=9.62, $P<0.005$, two-way ANOVA). However, 5β-pregnanolone threshold was not significantly altered by 20% β-cyclodextrin pretreatment at 3.0 ml $kg^{-1}$ compared with untreated controls (least- significant difference test). In order to avoid an effect of the vehicle, the amount of β-cyclodextrin used during pregnenolone and pregnenolone sulphate pretreatment was maintained at less than 3.0 ml $kg^{-1}$. Doses of pregnenolone 3.5, 7.0 and 14.0 mg $kg^{-1}$ were tested. Pregnenolone sulphate pretreatment was performed at doses of 4.5, 9.0 and 18.0 mg $kg^{-1}$, which were equimolar to the corresponding doses of pregnenolone. Eight rats were used in each dose group. As a control, eight rats were pretreated with β-cyclodextrin 3.0 ml $kg^{-1}$ in both the pregnenolone and pregnenolone sulphate parts of

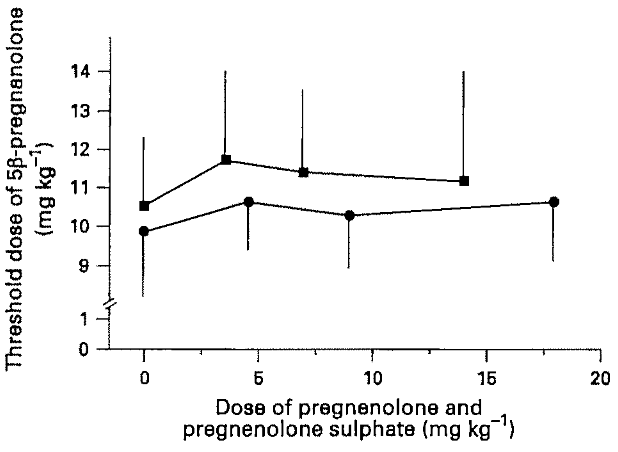

*Figure 2* Relationship between dose of pregnenolone (■) or pregnenolone sulphate (●) and threshold doses of 5β-pregnanolone at silent second.

the experiment. We found that neither pregnenolone nor pregnenolone sulphate significantly altered the threshold doses of 5β-pregnanolone at SS ($F_{3,27}$=1.07, $P$=0.38 and $F_{3,27}$=0.43, $P$=0.74, respectively) (fig. 2).

Doses of pregnenolone 14.0 mg kg$^{-1}$ ($n$=9) and pregnenolone sulphate 18.0 mg kg$^{-1}$ ($n$=9) were also used to study the interaction of the two neurosteroids with hexobarbitone-induced anaesthesia. As a control, nine rats were pretreated with β-cyclodextrin 3.0 ml kg$^{-1}$, 15 min before infusion of hexobarbitone. We found that the threshold doses and cortex concentration of hexobarbitone in the control group (111.3 (8.9) mg kg$^{-1}$ and 92.4 (4.7) μg g$^{-1}$, respectively) were not significantly different from those in the pregnenolone (117.5 (10.9) mg kg$^{-1}$ and 93.4 (8.5) μg g$^{-1}$) and pregnenolone sulphate (105.1 (13.7) mg kg$^{-1}$ and 90.0 (4.9) μg g$^{-1}$) groups.

## Comment

We have previously used a protein vehicle, albumin, as steroid solvent and observed that an albumin preparation of 5α-pregnanolone was more potent than its lipid preparation in inducing anaesthesia.[5] When we investigated the effect of albumin on the anaesthetic potency of hexobarbitone, threshold doses of hexobarbitone at SS increased in the pregnenolone treated group in the same way as in the control group given the corresponding volume of albumin. However, hexobarbitone concentrations in plasma, fat and four parts of the brain did not change significantly. This indicated that brain sensitivity to hexobarbitone was stable regardless of the increasing doses of albumin. Albumin as a vehicle might cause volume expansion of the blood compartment, thereby diluting the CNS depressant drug in serum. Our results from an interaction study between pregnenolone, pregnenolone sulphate and hexobarbitone differed from those of Majewska and co-workers[2] who observed that pregnenolone sulphate 8.6–16.8 mg kg$^{-1}$ i.p. reduced pentobarbitone-induced anaesthesia time by 17–37%. Differences between results obtained when studying induction of anaesthesia compared with those from experiments examining anaesthesia time could be caused by several factors unrelated to changes in brain sensitivity in response to the agents tested, such as elimination rate of the anaesthetic, hypothermia, acute tolerance or pharmacokinetic properties of the substances used during pretreatment. These factors are unrelated to changes in brain sensitivity which may have been induced by the pretreatment.

If pregnenolone sulphate interacts with the steroid recognition site on the GABA$_A$ receptor complex and thus alters the sensitivity to anaesthetic agents acting on the GABA$_A$ receptor, it would be expected that the sensitivity to 5β-pregnanolone should be influenced more profoundly than that of barbiturates.[1] However, we studied the influence of pregnenolone and pregnenolone sulphate on induction of 5β-pregnanolone-induced anaesthesia. However, we found no interaction despite maximal doses clearly within the range used by Majewska and co-workers.[2] The interval between pregnenolone sulphate pretreatment and infusion of 5β-pregnanolone may be critical for drug interaction. Therefore, we have also studied intervals of 5, 15, 30 and 45 min between pretreatments and 5β-pregnanolone infusions. The threshold doses at SS did not differ significantly between rats with different delay times (data not shown). The lack of effects in our rat strain could be a result of minimal brain extraction of pregnenolone sulphate because of its low lipophilicity. However, determination of pregnenolone sulphate at SS revealed a concentration of up to 200 ng g$^{-1}$ in some brain parts in rats pretreated with pregnenolone sulphate 18.0 mg kg$^{-1}$ (data not shown). This is the concentration at which pregnenolone sulphate may be expected to have effects on the CNS.[6] Furthermore, this concentration of pregnenolone sulphate was approximately 100 times less compared with brain concentrations of 5α-pregnanolone, a steroid anaesthetic related to 5β- pregnanolone, at induction of SS with a dose of 8 mg kg$^{-1}$.[5] Thus it was not strange that no interaction was observed between pregnenolone sulphate and 5β-pregnanolone.

Another possibility which could explain the dose-dependent antagonistic effect of a pregnenolone sulphate solution is that the vehicle could have increased the volume of the blood compartment, not only in our experiments, but also in those of Majewska and co-workers.[2] Pregnenolone sulphate has been reported to interact with the GABA$_A$ receptor in a manner opposite to that of 5β-pregnanolone in the micromolar concentration range.[1] However, Gee, Joy and Belelli[6] demonstrated that pregnenolone sulphate at submicromolar concentrations had anticonvulsive activity in mice. Some steroids could have both excitatory and anticonvulsive effects in the CNS. It is also possible that the magnitude of the dose could be important as several CNS depressant drugs have excitatory effects at low doses.

## Acknowledgements

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# Antagonism of suxamethonium-induced jaw muscle contracture in rats

Y. SHI, R. J. STORELLA, M. M. KEYKHAH AND H. ROSENBERG

## Summary

Masseter muscle rigidity (MMR) induced during general anaesthesia by suxamethonium is a clinical problem that may interfere with tracheal intubation. We have investigated the relation between twitch tension and contracture response to suxamethonium in rats. Rats were anaesthetized with 1% halothane (1.35 MAC). Jaw muscle temperature was maintained at either 37 or 41 °C while rectal temperature was kept at 37 °C by radiant heat. Twitch tension was produced by nerve stimulation at 0.2 Hz. Rats were pretreated with either a low dose of vecuronium (0.03 mg kg$^{-1}$) or dantrolene (0.8 mg kg$^{-1}$). Thereafter suxamethonium 750 μg kg$^{-1}$ was administrated i.v. Low-dose vecuronium pretreatment significantly (90%) decreased suxamethonium-induced jaw muscle contracture (JMC) with minimal (3%) twitch block during local hyperthermia. Low-dose dantrolene pretreatment also reduced JMC (81% at 37 °C and 82% at 41 °C) while decreasing twitch by 30% at 37 °C and 31% at 41 °C. Both vecuronium and dantrolene at doses that minimally depressed the twitch response antagonized suxamethonium-induced JMC. We speculate that pretreatment with low-dose vecuronium decreases suxamethonium-induced MMR clinically. (*Br. J. Anaesth.* 1997; **78**: 332–333).

**Key words**
Anaesthetics volatile, halothane. Hyperthermia, malignant. Complications, masseter muscle rigidity. Neuromuscular block, suxamethonium.

Suxamethonium may produce masseter muscle rigidity (MMR) during induction of anaesthesia and cause difficulty in tracheal intubation.[1] Previous laboratory studies showed that suxamethonium can induce jaw muscle contracture (JMC) during halothane anaesthesia in rats. The interaction between local hyperthermia of the jaw muscle and halothane can greatly increase suxamethonium-induced JMC.[2 3] Vecuronium is a non-depolarizing neuromuscular blocking agent while dantrolene is used in the prevention and treatment of malignant hyperthermia (MH). The purpose of the study was to examine if low doses of vecuronium and dantrolene, which have minimal effects on twitch, can block JMC in the rat.

## Methods and results

The study was approved by the University Animal Welfare Committee. We designed two sets of experiments using similar methods. Male Wistar–Furth rats (278–440 g) were anaesthetized with 1% halothane (1.35 MAC). After tracheotomy and establishing mechanical ventilation, the right femoral vein was cannulated for drug administration. Isometric jaw muscle tension was recorded via a tension transducer connected to the lower incisors. Twitch tension was produced by bilateral supramaximal mandibular nerve stimulation (0.2 Hz). Jaw muscle temperature was maintained at 37 °C (normothermic) or 41 °C (hyperthermic) by radiant heat and monitored by a temperature probe (Mon-a-Therm 6501) which was secured into the left jaw muscle while rectal temperature was maintained at 37 °C by a heat lamp.

In preliminary experiments, the dose effects of vecuronium and dantrolene on twitch tension and suxamethonium-induced JMC were examined to obtain the correct doses which could maximally block JMC with minimal inhibition of twitch tension. In the first set of experiments vecuronium was tested. Rats were allocated randomly to one of two groups ($n=6$ each): vecuronium and control groups. Vecuronium 0.03 mg kg$^{-1}$ was administered i.v. 40 s before administration of suxamethonium 750 μg kg$^{-1}$. Saline was injected i.v. before suxamethonium injection in the control group. Jaw muscle temperature was maintained at 41 °C with rectal temperature kept at 37 °C. In the second set of experiments, dantrolene was tested. Rats were allocated randomly to one of four groups ($n=6$ each): control hyperthermic, control normothermic, dantrolene hyperthermic and dantrolene normothermic groups. Dantrolene 0.8 mg kg$^{-1}$ or saline was administered i.v. 5 min before administration of suxamethonium 750 μg kg$^{-1}$ i.v. The percentage of twitch tension block by vecuronium or dantrolene and peak contracture after suxamethonium were measured. Data

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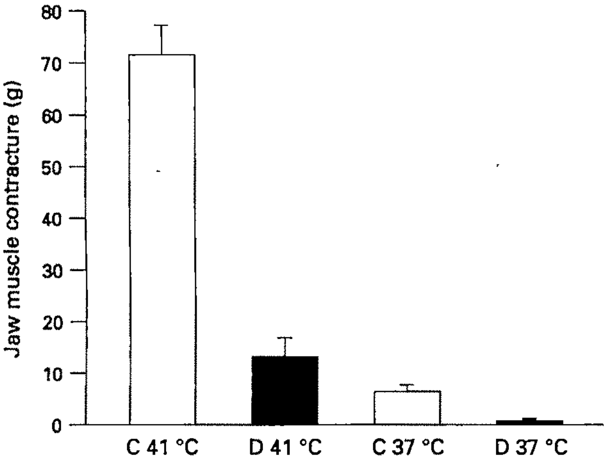

*Figure 1* Suxamethonium-induced jaw muscle contracture was significantly different among control hyperthermic (C 41°C), dantrolene hyperthermic (D 41°C), control normothermic (C 37°C) and dantrolene normothermic (D 37°C) groups. Both dantrolene and jaw muscle temperature had significant effects on the differences ($P<0.01$, ANOVA).

are presented as mean (SEM). Student's *t* test and two- factor ANOVA were used. $P<0.05$ was considered significant.

In the absence of pretreatment, suxamethonium produced JMC. Low-dose vecuronium (0.03 mg $kg^{-1}$) had a significant effect on JMC but little effect on twitch. Compared with control, suxamethonium-induced JMC was reduced by approximately 90% (48 (7.3) *vs* 4.7 (1.0) g; $P<0.01$, *t* test). In contrast, twitch tension was blocked minimally (3 (1.5) %) by vecuronium.

Low-dose dantrolene (0.8 mg $kg^{-1}$) also had a significant effect on JMC but modest effect on twitch (fig. 1). Compared with the control groups, dantrolene pretreatment reduced suxamethonium-induced contracture by 81% (1.3 (0.1) *vs* 7.0 (1.1) g) under normothermic conditions and by 82% (13 (4.4) *vs* 72 (6.3) g) under hyperthermic conditions ($P<0.01$, ANOVA). Twitch tension block by dantrolene was also similar in both hyperthermic and normothermic groups (31 (2.6) *vs* 30 (1.7) %). As elevation in jaw muscle temperature increased suxamethonium-induced JMC by approximately 10-fold in both the control (7.0 (1.1) *vs* 72 (6.3) g) and dantrolene (1.3 (0.1) *vs* 13 (4.4) g) groups, dantrolene 0.8 mg $kg^{-1}$ did not alter the temperature dependent effect of suxamethonium-induced JMC.

## Comment

Dantrolene is used in the prevention and treatment of MH. We found that low-dose dantrolene (0.8 mg $kg^{-1}$) pretreatment also greatly inhibited suxamethonium-induced JMC while only modestly blocking twitch. Interestingly, the percentage diminution of JMC was similar both with and without dantrolene pretreatment, indicating that dantrolene does not alter the temperature dependence of suxamethonium-induced JMC.

Vecuronium is often used in low doses to reduce the cholinergic agonist action of suxamethonium (i.e. fasciculations). We found that low-dose vecuronium (0.03 mg $kg^{-1}$) pretreatment, which only minimally affected twitch, almost completely blocked suxamethonium-induced JMC. The explanation for the greater sensitivity of suxamethonium-induced contracture than twitch to vecuronium may be that JMC is caused by a halothane–suxamethonium interaction at extrajunctional receptors, as contracture is more sensitive to non-depolarizing block than twitch because the latter has a "margin of safety".[4]

Smith and colleagues[5] reported that increases in muscle tension of approximately 50% are a normal response to suxamethonium in children and suggested that MMR may be considered as an exaggerated form of the normal pharmacological effect of suxamethonium. Smith and colleagues found that a sub-paralysing dose of tubocurarine (0.05 mg $kg^{-1}$) was ineffective in preventing the increase in suxamethonium-induced masseter muscle tension in children. If we consider that the contracture at normal jaw muscle temperature is a "normal response" to suxamethonium, it is reasonable to propose that the contracture at elevated jaw muscle temperature (which is 10-fold the contracture at normal temperature) is an "exaggerated response" to suxamethonium. Therefore, we believe that our findings are more relevant to generation of MMR.

We conclude that both dantrolene and vecuronium, at doses that minimally depressed twitch response, antagonized suxamethonium-induced JMC. JMC may be mediated by extrajunctional acetylcholine receptors in rats. We also speculate that pretreatment with small doses of vecuronium decreases suxamethonium-induced MMR clinically.

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CASE REPORT

# Lumbovertebral syndrome after repeat extradural blood patch

J. H. McG. Palmer, D. W. Wilson and C. M. Brown

## Summary

We describe an obstetric patient who developed incapacitating headache after inadvertent dural tap and was treated with repeated blood patching. She subsequently developed severe lumbar back pain which, after exclusion of suspected extradural abscess, was treated successfully with simple analgesics and physiotherapy. Two possible explanations are offered to account for her symptoms. We compare this case with others in the literature. (*Br. J. Anaesth.* 1997; **78**: 334–336)

**Key words**
Anaesthetic techniques, extradural. Complications, lumbovertebral syndrome. Anaesthesia, obstetric.

## Case report

A 39-yr-old woman was admitted for elective lower segment Caesarean section (LSCS) at 36 weeks' gestation. She was seen by an anaesthetist before operation and decided to have the procedure under regional anaesthesia. During the performance of lumbar extradural block an inadvertent dural tap occurred. On the advice of the consultant anaesthetist present, the extradural catheter was introduced into the subarachnoid space, an intrathecal block performed using 0.5% "heavy" bupivacaine 2 ml, and continuous spinal infusion of 0.125% bupivacaine 2 ml $h^{-1}$ containing fentanyl 1 $\mu g$ $ml^{-1}$ started. This resulted in a good block to cold sensation extending from T3/4 to S1 bilaterally. This procedure and subsequent Caesarean section were uneventful and the patient was allowed to return to the postnatal ward with advice to remain supine for several hours, and she received laxative therapy and a generous i.v. fluid therapy regimen (3800 ml over the next 24 h). The spinal infusion was continued for 12 h at which time, because of the change in level of anaesthetic cover at that time (23:00), i.v. PCA morphine was started and the spinal catheter removed. She was reassessed at this time and had neither symptoms of post-dural puncture headache (PDPH) nor pain. However, later the following day she developed both frontal and occipital headache with neck pain and 48 h after LSCS the decision was taken to perform extradural blood patching. This was performed by a consultant using 12 ml of autologous blood at the same lumbar interspace (L3/L4) as the dural tap, with immediate improvement in her symptoms. Blood was taken for cultures at the same time. After this the patient remained recumbent for 1 h.

Follow-up of the patient by anaesthetic staff showed an encouraging improvement of her headache with only very mild symptoms, allowing her to function normally, but 2 days later, just before discharge, the same headache abruptly recurred. Physical examination at this time was unremarkable with no local back problems, pyrexia or cranial nerve signs.

She was treated conservatively for a further 48 h with no improvement in symptoms and after further discussion repeat blood patching was performed. This was also performed by a consultant anaesthetist, on this occasion using the interspace above and an increased volume of 17.5 ml of autologous blood. Blood for cultures was again obtained at this time.

She did not obtain complete relief of her headache immediately, but she did report considerable improvement which allowed her to nurse her baby and return to full mobility. Anaesthetic follow-up at the time of discharge the following day showed continued improvement in her PDPH symptoms. She was instructed to return to the anaesthetic clinic 3 days later and encouraged to report daily by telephone to the on-call anaesthetic team.

At her clinic appointment she reported that her headache had disappeared, but that she had developed intermittent bilateral buttock pain, which made it difficult to walk. She also said she became "very sweaty" when walking. The consultant examining her found no positive physical signs and advised her to use simple analgesics and contact us if the problem did not resolve. She telephoned the consultant on-call 48 h later, obviously in severe distress, and complaining of severe back pain which she described as being low down "in her bottom" with radiation to the front of her thighs. This pain came on with walking, lasted only a few seconds, but was so excruciating that she would collapse without assistance. She was asked to come in immediately for review.

She was questioned and described little or no pain while seated or recumbent, but that the pain would come on suddenly if she rose from a chair, and

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would increase in severity after she took a few steps. She described the pain as being of a throbbing nature, similar to a very strong cramp but without any shooting character. The pain extended across the upper buttocks and radiated into the anterior thighs. She stated it was the pain in her back rather than weakness of the legs that caused her to collapse. She had no fever or rigors but reported diaphoresis with minimal exertion. She denied symptoms of urinary or faecal retention/incontinence and reported no paraesthesia. She was very distressed by the pain and frequently tearful.

On examination she had an awkward and hesitant gait limited by pain to a few steps and needed assistance to climb onto the examination couch. She was afebrile (37.1 °C) and the extradural puncture site was not tender, with no warmth, swelling or bruising present. Palpation of her back revealed tenderness over the L3, 4, 5 facet joints, particularly on the left, and marked left paravertebral muscle spasm. Both sacroiliac joints were non-tender on springing the pelvis. Straight leg raising was diminished on both sides and restricted to 45°, with pain in the back preventing further hip flexion. The pain was not exacerbated by ankle dorsiflexion, which suggested it was not caused by nerve root compression or disc prolapse. Reflexes, tone and sensation were normal in both lower limbs. She had reduced back flexion to approximately 80°, but extension, lateral flexion and rotation were normal.

Both x-rays and CT scan of her lumbar spine were normal, as was her full blood count. Blood cultures performed at the time of patching were negative.

A provisional diagnosis of back pain caused by lumbar facet joint irritation was made and she was prescribed simple analgesics and referred for physiotherapy aimed at reducing the paravertebral muscle spasm and mobilizing her facet joints. She was given a full explanation of her problem and reassured about worries she had of a more serious cause for her symptoms.

She showed marked improvement with physiotherapy, to the extent that she was discharged from the physiotherapy outpatient clinic after three visits. At follow-up by telephone 1 month later she was cheerful and reported no headache, good mobility and minimal back symptoms brought on by awkward posture which were similar to the non-specific back pain she had suffered as a typist a few years previously.

## Discussion

Inadvertent dural puncture occurs in approximately 1.3% of obstetric extradurals, the rate being affected by the experience of the operator and factors relating to the technique and patient.[1] In our case the patient significantly exceeded her ideal weight (113 kg for a height of only 166 cm) which made extradural puncture difficult and the extradural was sited by an SHO who had performed 150 extradurals. The rate of PDPH with a 16-swg Tuohy needle has been reported as 81%.[1] Extradural blood patching is most successful if used after conservative methods have failed rather than as a prophylactic measure, when success rates are lower,[2 3] although this has not been found by all investigators.[4] The optimum volume of blood to use remains a choice for the individual anaesthetist, with volumes of 5–15 ml being common[2–6] and one study[5] found no benefit in exceeding 10 ml. Overall the success rate of a first blood patch is high, with up to 96% of patients reporting complete initial disappearance of symptoms and 86–89% of patients satisfied 4 weeks after their first patch even if the headache had not completely gone.[5] After failure of a first blood patch the choices are less obvious, with some authors recommending repeat patches, others normal saline infused extradurally[6 7] and even the use of extradural dextran infusions.[8] We chose the repeat patch as the first had been initially successful. There are reported cases of back pain after initial blood patching[9–11] but we could find only one which closely resembled ours. In their article[9] Seeberger and Urwyler described the case of a 40-yr-old woman with remarkably similar symptoms. She also had a previous history of low back pain, had been in a clerical occupation and her pain after blood patching matched the extent and distribution in this case, particularly radiation to the anterior thigh. The two women both complained of sweating, although in their case this was nocturnal.

The major differences were that their patient was non-obstetric and had a unilateral plaster cast which, together with the abnormal gait caused by the use of crutches, was thought to be a possible cause of the back pain. They also believed that the relatively large volume of blood injected (25 ml) might have been a contributory factor. In our case the second blood patch volume was 17.5 ml and the initial blood patch was 12 ml, both well below the volume used by Seeberger and Urwyler and would tend not to support their view. One other possible cause for back pain has been suggested by Beards and colleagues[12] who demonstrated by magnetic resonance imaging extensive subcutaneous spread of blood after blood patching. They felt this might contribute to back pain.

The immobilization of our patient for the purpose of initial conservative treatment, prolonged after failure of the first blood patch, may have also encouraged abnormal back posture, which ultimately caused the facet joint irritation symptoms. In addition, daily visits by an anaesthetist and our obvious concern about her recovery may have reinforced any emotional factors thus exacerbating her symptoms. Back pain after childbirth is a well recognized and frequent complaint. One study of more than 1000 women who were questioned about back pain with onset before or during pregnancy or with onset post-partum, revealed that the overall incidence of back pain 1–2 months post-partum in this population was 44%. Predisposing factors were a previous history of back pain, younger age and greater weight.[13] For those with new onset post-partum back pain, predisposing factors were greater weight and shorter stature. Our patient fitted into this category.

In conclusion, we suggest that for those women likely to develop back pain post-partum who require extradural blood patching, prophylactic physiotherapy and information on posture and lifting should be offered. Also, in this group of women, it would seem sensible to avoid immobilization as part of the conservative treatment of PDPH.

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# CORRESPONDENCE

## Removal of LMA in children

Sir,—The article of Kitching, Walpole and Blogg[1] investigating removal of the laryngeal mask in anaesthetized and awake children merits further discussion. At our hospital we routinely use the laryngeal mask airway (LMA) in the general paediatric population for various ear, nose and throat (ENT) procedures.[2] Our standard practice is in accordance with those of both the inventor and the manufacturer of the masks.[3] The LMA is left *in situ* until the patient regains protective airway reflexes unless problems arise before this time requiring active airway management. We agree that children have an increased incidence of airway complications when recovering from anaesthesia compared with the adult population[4] and appreciate the challenging period this can be. For this reason we have conducted a prospective audit into the clinical use of the LMA at our hospital. As part of this we have examined specifically the recovery phase of anaesthesia with the LMA in paediatric patients. This information should add to the debate which this article will generate.

Currently we have audited 140 paediatric patients aged 1–14 yr old, weighing 5–45 kg, undergoing routine ENT procedures. Anaesthesia was induced with propofol i.v. in 112 cases and sevoflurane in the remaining 28 patients. Each LMA was inserted by the classical method, as described by Brain,[3] and only reinforced masks[5] sizes 2, 2.5 and 3 were used. All were left *in situ* at the end of the procedure to allow full return of airway reflexes and any airway complications before or after removal of the LMA were noted. A record was also kept of who removed the mask and depth of anaesthesia on removal.

A total of 126 (90%) children had a totally uneventful recovery period with no airway complications. In those cases where complications occurred, the commonest problem was either coughing or retching associated with impending mask expulsion by the patient. The overall incidence of airway complications with the LMA during recovery was as follows: seven (5%) patients coughed, four (3%) retched and three (2.5%) had laryngospasm. There were no episodes of aspiration or loss of airway. The LMA was removed by the child in 28 (22%) cases, recovery nurse in 89 (70%) cases and the anaesthetist in nine (8%) cases. None of the masks was removed at a deep stage of anaesthesia; the conscious level of the patient on removal of the LMA was recorded as light (i.e. responded to physical stimulation but inappropriate response to verbal command) in 36 (28%) cases and awake (i.e. appropriate response to verbal commands) in 90 (72%) cases. The three cases of laryngospasm occurred in patients undergoing adenotonsillectomy and all presented soon after cessation of anaesthesia, with the LMA being removed by the anaesthetist in two of these cases. In two patients the LMA lodged in the oropharynx on attempted removal but in both cases the mask was soon extricated with gentle manipulation. One case of partial airway obstruction occurred when the child displaced the bite block and consequently bit on the LMA tube; this resolved on awakening. Only three (2%) patients required the LMA to be replaced with an oral tracheal tube for either inadequate airway maintenance or mechanical problems during the procedure.

The results of our ongoing audit on the use of the LMA in the ENT paediatric population shows a lower overall incidence of airway complications than the study by Kitching, Walpole and Blogg. Our values bear more relation to those of Mason and Bingham[6] who studied the use of the LMA in 200 paediatric patients. They reported 12 (6%) cases of coughing, 11 (5.5%) of biting, five (4%) of laryngospasm, four (4%) of retching and three (3.5%) of vomiting during the recovery phase. These authors left the LMA *in situ* in all cases until return of laryngeal reflexes and expulsion of the mask by the patient. Laffon and colleagues[7] investigated airway complications after anaesthetized compared with awake removal of the LMA in 60 children. This study demonstrated a lower incidence of airway complications in both the anaesthetized and awake groups than the study of Kitching, Walpole and Blogg and, more importantly, detected no significant difference between the two groups in individual airway complications. Again, in this study, the LMA remained *in situ* until the children demonstrated recovery of airway reflexes and had opened their eyes or mouth. Both of these previous studies and our current LMA audit have demonstrated a lower incidence of airway complications with the LMA during recovery than the study of Kitching, Walpole and Blogg. Several reasons may explain this variation in clinical experience with the LMA.

First, the LMA was removed when the child had awakened *sufficiently to swallow*. We contend that this depth of anaesthesia does not equate with either full return of airway reflexes or an awake state. The presence or return of swallowing in the anaesthetized patient with the LMA *in situ* is associated with an inadequate or "light" depth of anaesthesia.[8] The mask was therefore removed at too early a stage in the recovery process, associated with increased airway reflexes and complications. Second, the authors failed to mention if the LMA cuff was deflated before removal. Brain has stated previously that it is best to leave the cuff inflated until the mask is ejected spontaneously and to monitor cuff pressure via the pilot balloon during recovery.[9] A third possible cause of airway stimulation might have been inadequate peroperative analgesia as not all children received a caudal anaesthetic and the number in each group receiving such analgesia was not clearly stated. The study design also included rectal diclofenac on arrival in the recovery room but because of the rapid recovery time of sevoflurane[10] the children may have been in a light plane of anaesthesia while the suppository was administered. Any form of stimulating procedure at such a stage of anaesthesia can be associated with reflex airway responses. Finally, the authors failed to mention one of the major advantages offered by the LMA during recovery, namely maintenance of a patent airway thus decreasing the incidence of airway manoeuvres required during this period.[2] The importance of this benefit cannot be over-stated.

Avoidance of coughing and retching during recovery from ENT and plastics anaesthesia is important in order to prevent venous congestion and the potential for subsequent haemorrhage. ENT practice is associated with a higher incidence of airway complications than other areas of anaesthesia and the need for airway control in this group of patients is critical if such problems are to be avoided. We suggest from our experience that the LMA should be left *in situ* at the end of operation and remain so until it is expelled spontaneously by the awake child. There is a need for increased education of recovery staff in the correct management of the recovery phase with the LMA and non-intervention, avoiding excessive stimulation and suctioning is recommended if the full potential of the LMA is to be achieved.

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Sir,—We thank Drs Parry, Glaisyer and Bailey for their interest in our article and for raising some points of difference between us.

The patients in our study received a "standardized" anaesthetic. Children who could not have the particular anaesthetic technique were excluded. All children had inhalation induction with halothane as we wished to eliminate the different effects on airway irritability possessed by various i.v. induction agents and other volatile agents. Because all patients were undergoing a plastic surgery procedure on the perineum or lower limb, a caudal or local block was performed for intraoperative and postoperative pain relief. We encountered no problems with insertion of the diclofenac suppositories in either the "deep" or "awake" group, probably because of the block. The entire anaesthetic technique was designed to make the time of removal of the LMA the only variable. The cuff was deflated before removal. Sevoflurane was not available.

Although Parry, Glaisyer and Bailey described a lower overall incidence of airway problems than in our study, we noted that two of their 140 patients required tracheal intubation whereas none of our 60 children did. However, patients in our study differed from those reported by Parry, Glaisyer and Bailey in being younger, not undergoing airway surgery and all having had antisialogogue premedication (oral atropine). Monitoring in the recovery period differed between these studies as all of our patients had continuous observation by one of the authors in addition to pulse oximetry. It is regrettable that Parry, Glaisyer and Bailey did not provide objective evidence of continued adequate oxygenation from $Sp_{O_2}$ measurements during recovery.

In our study of young children undergoing plastic surgery to the lower limbs and perineum, those in whom the LMA was removed at a deep plane had fewer coughing episodes compared with those removed on swallowing, however, coughing was not associated with other adverse respiratory events or hypoxia. In practice, swallowing normally immediately precedes wakefulness.

We agree that avoidance of coughing and retching is important in the recovery period to prevent complications such as haematoma formation After upper airway surgery, as Parry, Glaisyer and Bailey suggest, it may be best to leave the LMA *in situ* until the patient is awake, as any blood in the airway pools above the LMA and is scooped up on removal. Nonetheless, Parry, Glaisyer and Bailey removed the LMA before the child awoke in 28% of cases.

The lessons to be learned are that the LMA can be removed "deep" or at an "awake" plane, but coughing is most likely if swallowing reflexes have returned. When airway complications in the recovery phase are to be investigated, an anaesthetic technique should be chosen to reduce the number of variables to a minimum.

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## Predicting difficulty—clinical indices and their statistical equivalents

Sir,—We were interested in the article by Ramadhani and colleagues[1] and their attempt to further familiarize clinicians with statistical definitions such as sensitivity, specificity, positive predictive values, etc, in respect of clinical tests for predicting difficult intubation. These definitions have appeared repeatedly in this type of article, despite being readily accessible in most statistical texts. The clear implication is that they are not intuitively obvious to clinicians and in presentations to our department we have suggested (slightly tongue in cheek) alternative clinical indices which may be considered to have more obvious clinical relevance and which may be described in terms of standard statistical definitions.

We need to start with some assumptions which although not necessarily clinically obvious also generally apply to standard statistical tests. First, prediction and difficulty assessment need to be considered as either easy or difficult with no indeterminate or intermediate categorization options. Second, we have to assume that these defined states are both absolute and universal (i.e. experienced and trainee anaesthetists would recognize the same classification and make the same judgements). Finally, we relate the proposed clinical indices to a non-Calman situation where the "on-call" trainee anaesthetist works without direct supervision and the experienced colleague is available to be called in from home.

For the trainee, clinical responsibility with regard to prediction of difficulty should end when difficulty is diagnosed. We expect the experienced colleague to come from home and deal with all such cases or at least take clinical responsibility for whatever happens From the trainee's point of view, continuing responsibility is important in respect of the cases predicted as easy. The trainee anaesthetist's nightmare (TAN) is the number of cases predicted to be easy but which turn out to be unexpectedly difficult relative to the total number predicted as easy. Referral to standard statistical definitions shows TAN=1−NPV (NPV=negative predictive value, the number of easy intubations correctly predicted relative to the total number of intubations predicted to be easy). In a similar manner, the experienced anaesthetist's tribulation (EAT) is the number of cases predicted to be difficult which turn out to be easy relative to the total number predicted as difficult. This refers to the number of times attendance for allegedly difficult intubations will in fact be inappropriate. Again this is defined as EAT=1−PPV (PPV=positive predictive value, the number of difficult intubations correctly predicted relative to the number of intubations predicted to be difficult).

These "worse case" clinical indices may help clarify the clinical relevance of the statistical definitions which obviously came first and were not defined specifically for predicting difficult intubation. Another "*aide-mémoire*" which clinicians may find useful for remembering the statistical definitions is the graphical square box description in Altman's book.[2] This text also describes the limitations of each of the statistical indices and the importance of considerations of prevalence for the condition to which they apply.

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## Effect of amino acid infusion on body temperature during anaesthesia

Sir,—We were interested to read the study on the effects of preoperative infusion of amino acids in preventing postoperative hypothermia by Sellden, Bränström and Brundin.[1] We wish to comment on their conclusion.

The authors infused amino acid solutions (240 kJ $h^{-1}$) over 1–2 h before anaesthesia and compared the results with those from control patients who received saline, believing that preoperative administration of amino acids prevents anaesthesia-induced hypothermia.[1] In their previous study,[2] they suggested that peroperative amino acid infusion also prevented anaesthesia-induced hypothermia. In the present study,[1] they found that rectal temperatures increased significantly from the basal state during the first hour of amino acid infusion and decreased with the onset of anaesthesia. In the control group the decrease in temperature from the onset of anaesthesia was significantly greater than that in the amino acid-treated group.

We infused 335 kJ of amino acid solution during the first hour of anaesthesia to 25 patients and compared changes in nasopharyngeal and skin surface temperatures and the incidences of postoperative shivering with data from 25 control patients. In our study, nasopharyngeal and skin surface temperatures decreased in both groups during the first hour of anaesthesia. Nasopharyngeal temperatures decreased from 36.0±0.4 to 35.5±0.7°C in the amino acid-treated group and decreased from 36.2±0.4 to 35.7±0.5°C in the control group. Skin surface temperatures decreased from 32.2±1.2 to 32.1±2.1°C and from 32.4±1.6 to 32.5±1.7°C in the amino acid-treated and control groups, respectively. At the end of anaesthesia nasopharyngeal temperatures were 35.3±0.9°C in the amino acid-treated group and 35.5±0.7°C in the control group (ns). The incidences of shivering were similar in both groups (nine of 25 and seven of 25 in the amino acid-treated and control groups, respectively).

Our results do not confirm those of Selldén and collegues. Therefore, we believe that the effect of amino acid infusion on thermoregulation and its effect on preventing anaesthesia-induced hypothermia and postoperative shivering need further investigation.

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1. Selldén E, Branström R, Brundin T. Preoperative infusion of amino acids prevents postoperative hypothermia. *British Journal of Anaesthesia* 1996; **76**: 227–234.
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Sir,—Donmez, Şekerci and Arslan reported that infusion of an amino acid solution (composition not reported) during the first hour of anaesthesia did not prevent postoperative shivering or anaesthesia-induced reductions in nasopharyngeal or skin temperatures in 25 patients. The authors argue that these findings do not correlate with two of our published studies in which we demonstrated that i.v infusion of a mixture of 19 amino acids (Vamin, Pharmacia Upjohn, Stockholm, Sweden) stimulated oxidative heat generation to an extent that effectively prevented whole body hypothermia and postoperative shivering. We have recently published further confirmation of these findings,[1] and wish to offer the following comment.

(1) We do not know how nasopharyngeal temperature was recorded or what this temperature represents. The reported basal values, 36.0 and 36.2°C, seem low compared with normal mixed blood or body core temperatures, (2) the observed average anaesthesia-induced reduction in nasopharyngeal temperature did not exceed 0.5°C in any of the groups. If this value represents the whole body temperature change, the observation would indicate that the anaesthetic agent used (not reported) did not induce clinically significant hypothermia in any group; (3) a reduction in body core or mixed blood temperature of 0.5°C would hardly be expected to induce much generalized shivering Nevertheless 30% of patients shivered in response to this average decrease in nasopharyngeal temperature. Although individual correlations between temperature and shivering were not presented, the finding might further suggest that the changes in nasopharyngeal temperature did not adequately reflect whole body temperature changes, (4) the shivering incidence of nine of 25 in the amino acid-treated patients seems surprising not only because of the small temperature reduction. We have never recorded postoperative shivering in any patient subjected to our mode of intraoperative amino acid treatment; (5) an unchanged skin surface temperature may be a reasonable finding in view of the well known centrifugal redistribution of heat during general anaesthesia.

We appreciate the interest of Donmez, Sekerci and Arslan in this field and would like to encourage the authors to continued studies including rectal, oesophageal or mixed blood thermometry.

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## Anatomical configuration of the spinal column as determined by magnetic resonance imaging

Sir,— The anatomical configuration of the spinal column significantly affects the distribution of local anaesthetic solutions within the subarachnoid space. Hyperbaric anaesthetic solutions migrating cephalad, pool in the lowest region of the thoracic hollow under the influence of gravity[1] Textbooks of anaesthesia always describe that, in the supine position, the lowest point of the thoracic hollow is located at T5–6, a concept proposed by Barker in 1907.[2] However, no evidence exists to confirm this classical anatomical concept. We have demonstrated previously that the lowest point of the thoracic hollow determined by magnetic resonance (MR) imaging is located in the vicinity of T8 in Japanese healthy volunteers[3] and these findings do not agree with long-held concepts. However, differences in the curvature of the thoracic hollow may exist in subjects with different racial characteristics

Therefore, we attempted to examine sagittal MR images of the spinal column which are illustrated in MR imaging textbooks published in Europe and North America[4 5] There were no sagittal MR images to demonstrate that the lowest point of the thoracic hollow is located at T5–6. Of the eight images examined, the lowest point of the hollow was located at T7 in one, T8 in one, T8–9 in one, T9 in two, T9–10 in one and at T12 in two MR imaging provides precise anatomical information on the configuration of the spinal column in living subjects Consequently, the lowest point of the thoracic hollow in the supine position is unlikely to be located at T5–6, even in European and North American subjects.

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## Spinal anaesthesia with 0.25% hyperbaric bupivacaine for Caesarean section: effects of volume

Sir,—We read with interest the article by Chung and colleagues[1] comparing different volumes of 0.25% hyperbaric bupivacaine for Caesarean section using spinal anaesthesia and wish to make the following points.

(1) Although the authors used different volumes of 0.25% hyperbaric bupivacaine for spinal injection according to patient height, there is no evidence that varying the dose of local anaesthetic in this manner affects the final characteristics of a spinal block.[2] If in this study patient height did indeed influence the spinal block, there would have been differences between subgroups given the same volume. For example, did the characteristics of the block with bupivacaine 3.6 ml given to the subgroup of patients in group 1 who were 161–165 cm in height differ from the subgroup of patients in group 2, 156–160 cm in height, given the same volume of local anaesthetic. Unfortunately no analysis of these subgroups was presented.

(2) The results of this study are also not related directly to the effects of volume of 0.25% hyperbaric bupivacaine as suggested, as the same concentration of local anaesthetic was used

throughout the study. Therefore, as the volume of the spinal injection changed, so did the total dose of drug administered. The effect of volume independent of the actual amount of drug administered intrathecally was not compared. Many workers have demonstrated that the dose of intrathecally administered local anaesthetic is more important than volume.[3 4] Furthermore, there is evidence from the literature that the major factor affecting intrathecal spread of local anaesthetic in pregnant women at term is movement of the patient after spinal injection.[5] This is thought to result from extradural venous engorgement, secondary to vena caval compression while the patient is being turned, decreasing the volume of the dural sac and thereby leading to displacement and spread of the local anaesthetic solution. A recent MRI study appears to support this theory.[6]

(3) We also question the accuracy of the sensory block assessments. From the data in table 3, it appears that surgery started and ended approximately 16 min and 83 min, respectively, after spinal injection. We deduce from figure 1 that during these 67 min of operating time, pinprick assessments were still continuing Presumably, according to the dermatomal levels recorded within this period, pinprick testing was continuing within the area of a supposedly sterile operating field. Or, inconceivably, were the surgeons also undertaking intraoperative sensory testing?

(5) Finally, considering the high incidence of hypotension in group 3, we would have expected umbilical cord gas tensions to have been measured.

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6 Hirabayashi Y, Shimizu R, Fukuda H, Saitoh K, Igarashi T. Soft tissue anatomy within the vertebral canal in pregnant women. *British Journal of Anaesthesia* 1996; **77**: 153–156

Sir,—I thank Drs Bell, Fernando and Parry for their interest in our article.[1] Although the subgroups were small (only 10 cases), we analysed the differences in spinal block between all subgroups in groups 1 and 2, and groups 2 and 3, including subgroups given the same volume in different groups. There were no significant differences between all subgroups, except for subgroups with different heights, given different volumes. For example, the characteristics of spinal block with bupivacaine 3.2 ml in the subgroup of patients in group 1 who were 156–160 cm in height, differed from those with bupivacaine 4.0 ml in the subgroup of patients in group 2, 161–165 cm in height. The results support the concept that patient variables, especially height, are not important factors in determining the final characteristics of spinal block.[2]

Many workers[3 4] have demonstrated that the dose of intrathecally administered local anaesthetic is more important than volume or concentration in determining spread of anaesthetic solution in the CSF. However, other workers[5 6] have shown that increasing the volume administered into the subarachnoid space, especially with hyperbaric solutions, resulted in significantly greater cephalad spread. I agree that the effect of volume independent of the dose of drug administered intrathecally was not compared in our study. In the clinical dose range (10–15 mg) of 0.5% or 0.75% hyperbaric bupivacaine for spinal anaesthesia in Caesarean section, the volume does not exceed 3 ml. When 0.25% hyperbaric bupivacaine solution is used, a dose of 10–15 mg exists in a volume of 3.0–6.0 ml. The large volume of hyperbaric solution itself may influence the spread of local anaesthetics in CSF and final block, especially in the narrow subarachnoid space of the term parturient I think that the volume of hyperbaric spinal anaesthetic solution may be additive to the effects of gravity, position and dose.

As shown in tables 2 and 3, in all patients in groups 2 and 3, the regression times to T10 were more than 100 min and induction to end of surgery times were less than 85 min. Sensory block assessment was made easily in the flanks of patients without disturbing surgery in all patients in groups 2 and 3, but omitted during operation in approximately 50% of patients in group 1. However, the data did not influence the results, that is assessment of segmental spread of sensory analgesia (fig. 1) and regression time to T10 and L5 (table 2).

Umbilical cord blood analysis was not performed in this study and I think in retrospect that it would obviously have been better if these measurements had been made.

The aim of our study was to assess the safety and efficacy of 0.25% hyperbaric bupivacaine in glucose for spinal anaesthesia in Caesarean section. We found that if Caesarean section was undertaken with 0.25% hyperbaric bupivacaine for spinal anaesthesia, the volume required was at least 4.0 ml. Considering the quality of anaesthesia and incidence of hypotension, I think that 0.75% or 0.5% hyperbaric bupivacaine for spinal anaesthesia in Caesarean section is preferable to 0.25% hyperbaric bupivacaine.

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## Management of rhabdomyolysis

Sir,—Tuckey reported on the management of a patient who developed rhabdomyolysis after bilateral calf compartment syndrome resulting from the lithotomy position.[1] Such patients are at great risk of developing renal failure and Tuckey correctly stated that this may be reduced by aggressively promoting an alkaline diuresis with i.v. infusions containing bicarbonate and mannitol While I agree that such vigorous therapy should be given to prevent or limit further morbidity and mortality, therapy itself carries significant risk on three accounts.

First, the recommended volume infusions (12 litre day$^{-1}$)[2] may result in fluid overload in an actual or potential critically ill patient. Second, bicarbonate infusion can produce metabolic alkalosis. Alkalaemia is associated with increased mortality.[3] In response to metabolic alkalosis, compensatory hypoventilation may occur. It has been suggested that the magnitude of this response is limited by the imposition of hypoxic drive.[4] However, patients have been described with metabolic alkalosis and life-threatening hypoxaemia and hypercapnia [5–7] Metabolic alkalosis also impairs the relationship between ventilation and perfusion in the lung[8 9] and limits systemic oxygen delivery by promoting leftward shift of the oxyhaemoglobin dissociation curve. Third, infusion of large doses of mannitol has been implicated in provoking renal failure.[10]

Rhabdomyolysis is a critical illness. Its treatment may cause serious complications. Management in an intensive therapy unit is indicated.

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1. Tuckey J. Bilateral compartment syndrome complicating prolonged lithotomy position. *British Journal of Anaesthesia* 1996; 77: 546–549.
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Sir,—I thank Dr Ball for his interest in my case report of a patient who suffered bilateral compartment syndrome after prolonged lithotomy position. The discussion included a description of the treatment of renal failure associated with rhabdomyolysis which should commence with appropriate cardiovascular resuscitation and prompt fluid therapy to encourage urine flow. The renal protective effect of alkalinizing the urine has been demonstrated and results from the fact that urate and myoglobin are more soluble in alkaline urine. In the report I quoted Better,[1] who suggested a very aggressive regimen of fluid containing bicarbonate and mannitol, as an example of management guidelines. I acknowledge all of Dr Ball's comments as valid, but I wish to reply to each point in turn.

(1) The aggressive fluid regimen of Better[1] must be tailored to the status and response of the individual patient, using appropriate invasive cardiovascular monitoring in the intensive care in the critically ill patient. Better has stated elsewhere that if myoglobinuric acute renal failure has occurred, with reduced renal output, solute load should not be given and regular haemodialysis is indicated.[2,3]

(2) Bicarbonate therapy has been controversial for many years. Bicarbonate is used in two main contexts; first, in the treatment of metabolic acidosis and second, to facilitate alkaline diuresis to enhance excretion of poisons.

Regarding the treatment of acidosis, Arieff proposes that metabolic acidosis with increased anion gap can be classified into those conditions in which tissue hypoxia is either present or absent.[4] In general, when there is metabolic acidosis in the presence of tissue hypoxia, available tissue oxygen is not adequate for the individual's needs. Treatment of metabolic acidosis with sodium bicarbonate tends to limit further available oxygen because of its effect on the position of the oxygen dissociation curve, and this leads to increased production of lactate thereby worsening the metabolic acidosis. Arterial $P\mathrm{CO}_2$ is directly proportional to production of carbon dioxide and inversely proportional to alveolar ventilation.[5] Thus increased generation of carbon dioxide by administration of bicarbonate increases venous $P\mathrm{CO}_2$ if there is impaired cardiac output (resulting in decreased delivery of venous carbon dioxide to the lungs), or decrease in alveolar ventilation. Carbon dioxide readily diffuses into cells such that intracellular $P\mathrm{CO}_2$ approaches that of mixed venous blood. In a closed system, carbon dioxide accumulates after administration of bicarbonate thereby decreasing intracellular pH.[6] Several workers have demonstrated the negative inotropic effect of bicarbonate on the ischaemic myocardium.[7–9]

However, sodium bicarbonate may be beneficial to patients with metabolic acidosis in the absence of tissue hypoxia.[10] Bicarbonate dialysis is tolerated better than acetate dialysis without cardiovascular instability, in critically ill patients with cardiorespiratory dysfunction,[11–13] possibly because of a direct effect on myocardial contractility[14] or through the effects of alkalosis on peripheral resistance.[15]

Bicarbonate may be used in alkaline diuresis to enhance excretion of toxins, including myoglobin and salicylates. In the treatment of crush syndrome, Better has advocated early volume replacement and, if urine flow commences, he recommends forced solute alkaline diuresis to prevent myoglobinuric acute renal failure.[2,3] Noji recommends a similar technique.[16] Likewise, in the treatment of salicylate poisoning, alkalinization has been shown to enhance excretion of the poison.[17,18]

(3) Mannitol. Some workers who have described mannitol nephrotoxicity syndrome have found that it occurs only after high doses of mannitol (e.g. $>200$ g day$^{-1}$) but not at lower doses [19,20] It may occur at slightly lower doses if patients have pre-existing impaired renal function.[21] It appears that at a low dose mannitol acts as a renal vasodilator, while in high doses it is a renal vasoconstrictor.[19,21] Mannitol-induced acute renal failure responds promptly to haemodialysis with rapid resolution of anuria and recovery of renal function.[19–21]

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## Rocuronium and vecuronium

Sir,—Dr Schramm and colleagues demonstrated that rocuronium and vecuronium did not significantly affect intracranial pressure (ICP), MAP or CPP in a group of neurosurgical patients.[1] However, they then suggested that rocuronium may be used for neurosurgical patients without the risks associated with suxamethonium. Suxamethonium was not included in their study and the case against suxamethonium and adverse effects on ICP is probably overstated. Most studies have been performed on animals or on patients undergoing elective neurosurgery and should not be extrapolated to head injured patients, who are in the group most at risk from increased intracranial pressure.

In a recent prospective, randomized, double-blind crossover study, we compared the effects of suxamethonium or an equal volume of saline on cerebral haemodynamic state in 11 patients with severe head injuries.[2] All patients were sedated with i.v. infusions of propofol and morphine and their lungs ventilated mechanically in a regional neurosurgical intensive care unit. Mean age was 36 (range 17–70) yr and median GCS score 5 (range 3–8). Five patients had diffuse cerebral oedema, four were undergoing mechanical ventilation post-surgical evacuation of traumatic or subdural haematoma and two had traumatic intracerebral haematomas that did not require surgery. Mean baseline ICP was 12.5 (range 1–35) mm Hg and CPP 74.5 (55–96) mm Hg. There was no significant change in ICP or CPP after administration of suxamethonium or saline. This supports the work of Kovaric and colleagues who also showed no adverse effect of suxamethonium on ICP.[3] Rocuronium may have an onset of action approaching that of suxamethonium but its long duration of action makes it unsuitable for use as the first choice neuromuscular blocking agent in the management of patients with severe head injury when a full stomach is the rule rather than the exception. Suxamethonium remains the drug of choice for emergency intubation of severe head injuries with the proviso that it is preceded by adequate anaesthesia.

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Sir,—Regardless of the presence or absence of space-occupying intracranial lesions, suxamethonium in humans and animals produced significant increases in intracranial pressure (ICP) in many investigations. Lanier, Milde and Michenfelder[1] found that the increase in ICP with suxamethonium was accompanied by EEG arousal and an increase in cerebral blood flow (CBF). The increase in CBF was disproportionately greater than that expected from a concomitant increase in $Pa_{CO_2}$. In their subsequent study, they demonstrated that an increase in muscle spindle afferent activity paralleled the increase in CBF. Fasciculations in the muscles of the neck, causing stasis in the jugular veins, might also be a factor contributing to increased ICP with suxamethonium. Pretreatment with paralysing doses of pancuronium did not block afferent muscle activity or the CBF response. The increase in ICP was also not blocked by pretreatment with thiopentone.

In our institution we also studied the effects of suxamethonium on middle cerebral artery flow velocity using transcranial Doppler during intubation of the trachea in 10 head injured patients and found a significant increase in flow velocity after an i.v. bolus of suxamethonium (unpublished data until now). The mechanism of how suxamethonium influences ICP and CBF in humans remains uncertain. In contrast, there are as many studies concluding that ICP is not influenced by suxamethonium. Kovaric and colleagues[2] found that in brain-injured patients, suxamethonium did not alter cerebral blood flow velocity, cortical electrical activity or ICP. The literature on the effect of suxamethonium on ICP in animals and in humans has not provided firm indications that suxamethonium *per se* increases ICP Furthermore, inclusion of other drugs, differences in anaesthetic states and concurrent stimuli such as tracheal intubation further complicates analysis of the effect of suxamethonium on ICP. Increases in ICP seen with suxamethonium may also be caused by autoregulatory decreases in cerebral vascular resistance secondary to systemic hypotension. Braun and colleagues have made a valuable contribution to the literature, but despite many studies, including those of Braun and colleagues evaluating the effects of suxamethonium on ICP, controversy remains.

Respiratory problems and pulmonary infection frequently occur after head injury because of neurological dysfunction and laryngeal incompetence. Parr and Manara stated in their letter that rocuronium may have an onset of action approaching that of suxamethonium but its long duration of action makes it unsuitable for use as the first choice neuromuscular blocking agent in the management of patients with severe head injury. I cannot imagine any situation where early extubation of the trachea of a patient with severe head injury is planned and after intubation the clinical duration of action should be of minor concern as the effect of rocuronium on cerebral dynamics is not controversial. The only reason for the statement of Parr and Manara, therefore, is difficult airway management. Obviously we agree with them regarding patients with ileus, but those with severe head injury are at risk of aspiration with or without neuromuscular block. After intubation of the trachea of head injured patients using either vecuronium or suxamethonium, Redan and colleagues[3] concluded that paralysis and tracheal intubation in the emergency department is safe and may be a potentially life-saving manoeuvre in combat trauma patients. Nevertheless, a short onset of neuromuscular block is preferable as ventilation of the lungs of patients without intubation is risky. Intubation of the trachea of head injured patients in the emergency room should not be delayed as it may be for elective surgery or even for the patient with ileus. If intubation is impossible any other methods of airway access are required, for example emergency tracheotomy is indicated. Is suxamethonium superior because its duration of action lasts only a few minutes? The use of additional boluses of suxamethonium because of multiple intubation attempts may be accompanied by bradycardia, dual block and the other side effects of this drug.

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## Intraoperative heat administration

Sir,—The study by Beck and colleagues[1] claimed that warming with a water perfused oesophageal heat exchanger was significantly more efficient at preventing intraoperative cooling than warming using ventilation with warm humidified gases, which was statistically ineffective compared with no heating. However, the study design leaves this conclusion in some doubt.

Approximately 75% of the benefit of ventilation with warm humidified gas (airway warming (AW)) arises from prevention of loss of heat and moisture which occurs during respiration, with the remainder comprising condensation of hot water vapour and a very small amount from the increased gas temperature.[2] These last components are very small using a temperature of 39 °C, and the system used provides only approximately 85% of the thermal gain possible with the temperature recommended for use in the treatment of accidental hypothermia (i.e. 45 °C).[2] Unfortunately, in the two other groups the patients' lungs were ventilated with cool (room temperature) humidified gas. This would provide approximately 65% of the benefit achievable through AW. The study therefore compared the effect of 85% AW with 65% AW and 65% AW plus the oesophageal water warming system. A fair evaluation of the thermal value of AW would have required the two other groups to undergo ventilation with dry gas.

The gas temperature of 45 °C was selected for use during treatment of accidental hypothermia to avoid thermal damage to the mouth, pharynx and larynx when the system is used with a face mask. Because of its ample blood supply the respiratory tract below the larynx is very resistant to thermal damage. For example a patient at 24.3 °C undergoing ventilation for 24 h with saturated gas at 80°C suffered only mild, reversible damage to the respiratory tract.[2] Temperatures of 350 °C with dry gas or steam at 94–104 °C are needed to cause burning to the trachea.[3 4]

Finally, while the oesophageal water circulating system has been used effectively in the treatment of accidental hypothermia, it has disadvantages in that the equipment is suitable only for hospital use; there is a danger if the thin rubber balloon bursts or tears and the GI tract is flooded with water; insertion of the tube may be impossible if the patient's teeth are clenched; and there is the risk of triggering VF during insertion of the tube. Airway warming can be used in the field and does accelerate the rate of rewarming to a statistically significant degree.[5]

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Sir,—We thank Dr Lloyd for his interesting comments on our recently published study.[1] As clearly stated both in the title and in the text, our goal was to evaluate the efficacy of two warming methods in a clinical intraoperative setting, under standardized conditions. For this reason we chose a temperature level (39 °C) that may be judged too low, but which is higher than the usual temperature (30–34 °C) used during clinical anaesthesia. Moreover, we had to modify the Kontron Pearl humidifier that in its standard configuration for human use cannot exceed the 37 °C limit. We were definitely not willing to use the high temperature used by some for treating severe accidental hypothermia.

According to Hendrickx, Trahey and Argentieri[2] heat lost by one of our pigs (34 °C) undergoing ventilation at a $\dot{V}E$ of 4 litre min$^{-1}$ in dry air–oxygen at room temperature (24 °C) would be approximately 24.9 kJ h$^{-1}$. Humidification (100%) of inspired gas at room temperature (24 °C) would reduce heat loss to approximately 12.1 kJ h$^{-1}$ thus supplying (through condensation heat) less than 50% of heat loss. Humidification (100%) of inspired gas at 39 °C would provide approximately 20 kJ h$^{-1}$ (4.5 by increased gas temperature and 15.5 by condensation heat) which is 80% of the theoretical heat loss, approximately 8 kJ h$^{-1}$ (66%) more than humidification at room temperature. Therefore, humidification alone at room temperature would supply approximately 60% of the heat supplied by humidification at 39 °C.

However, the humidifier that was used in our experiment at 24 °C provided 80% relative humidity. In this situation, humidification of inspired gas at room temperature (24 °C) would reduce heat loss to approximately 14.6 kJ h$^{-1}$ thus supplying (through condensation heat) approximately 40% of heat loss or approximately 50% of the heat supplied by 39 °C humidification.

We agree with Dr Lloyd's conclusions; our experiment design did not allow comparison of warm humidification with a true control or with oesophageal warming alone. Our study compared the effect of ventilation with warm (39 °C) humidified (100%) gases, which is the 100% airway warming (AW) in this experiment, with 50% AW and 50% AW with oesophageal warming. A strict "*in vitro*" procedure should have supplied 0% AW during the warm humidification period.

We do not agree with Dr Lloyd's conclusion that our study is invalid. We planned to compare two heating systems in a controlled, standardized clinical condition; ventilation with dry gases does not exist now in clinical practice. Moreover, the gas from the hospital supply system has a relative humidity at room temperature of approximately 40%: this makes it impossible to use dry gas. In any case, by avoiding the use of a cold humidifier in the warm humidification period, we would have compared the effect of 100% AW with 25% AW and with 25% AW plus oesophageal warming.

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## Extraction of nitric oxide and nitrogen dioxide using molecular sieve 5A

Sir,—We read with interest the article by Poulton and colleagues[1] demonstrating the efficacy of a molecular sieve in absorbing both nitric oxide and nitrogen dioxide. However, we have some reservations with regard to the clinical applicability of this bench test.

We have recently used a molecular sieve 5A, pellet size 1.5 mm (SW Scientific, Bristol, UK) in a vertically mounted Waters canister (id 6.5 cm, length 10 cm) for the purpose of scavenging nitric oxide and nitrogen dioxide from the expired gas of patients receiving inhaled nitric oxide during mechanical ventilation. However, after using this method in two patients we have failed to demonstrate any efficacy.

Both patients were given inhaled nitric oxide via a Servo 900C ventilator (Siemens Elba AB, Sweden) and humidification of the inspired gas was provided by a heat and moisture exchanger. At each dose of nitric oxide (0, 2, 10, 20 and 0 ppm) both nitric oxide and nitrogen dioxide were measured in the expired gas immediately before and after the Waters canister using a calibrated electrochemical analyser (Micro Medical, Kent, UK). There was no measurable nitrogen dioxide with any dose of nitric oxide (table 1)

As can be readily seen we could not repeat the results of Poulton and colleagues. There are two possible explanations for this. First, we did not heat the zeolite to 400 °C for 24 h as we had been informed this was not necessary for efficacy (personal communication, SW Scientific). Second, the gas flowing through the Waters canister in our case not only contained nitric oxide and oxygen but also nitrogen, carbon dioxide and water. It is likely

*Table 1* Concentration of nitric oxide (NO) delivered to the patient, before molecular sieve 5A and after molecular sieve 5A

| | NO delivered to patient | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0 ppm | | 2 ppm | | 10 ppm | | 20 ppm | | 0 ppm | |
| | Patient 1 | Patient 2 | Patient 1 | Patient 2 | Patient 1 | Patient 2 | Patient 1 | Patient 2 | Patient 1 | Patient 2 |
| NO to patient | 0.4 | 0.2 | 2.4 | 2.1 | 10.2 | 10.5 | 19 8 | 20.6 | 0.5 | 0.4 |
| NO before sieve | 0 | 0 | 1.5 | 1.6 | 6.1 | 6.7 | 13 1 | 12.6 | 0 | 0 |
| NO after sieve | 0 | 0 | 1.4 | 1.4 | 5.1 | 5.2 | 12.1 | 11.8 | 0 | 0 |

that nitrogen, carbon dioxide and water alter the performance of the sieve and although this was mentioned by Poulton and colleagues the effect was not quantified. If it is really necessary to dry the zeolite by prolonged exposure to high temperature then the effect of expired water vapour on the function of the sieve may be significant. Further work is necessary to clarify these points.

In conclusion we agree that efficient scavenging of nitric oxide and nitrogen dioxide from a dry carrier gas comprising oxygen only can be achieved using a molecular sieve 5A but we have been unable to reproduce this result in clinical practice. We feel that extrapolation of this bench test result to clinical practice should be undertaken with caution.

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1. Poulton BB, Foubert L, Klinowski J, Latimer RD, Knowles PR, Vuylsteke A. Extraction of nitric oxide and nitrogen dioxide from an oxygen carrier using molecular sieve 5A. *British Journal of Anaesthesia* 1996; 77: 534–536.

Sir,—Thank you for the opportunity to respond to the comments of Findlay, Swart and Smithies relating to the use of molecular sieve 5A as a scavenging device in nitric oxide therapy. We feel that these authors have been misinformed about the crucial importance of dehydrating the sieve before use. As we have outlined in our article, the internal structure of the sieve is charged and therefore intensely hygroscopic; 125 g of dry sieve may be expected to take up 40 g of water. When the internal pores are saturated, the zeolite loses its ability to function as a sieve. Water vapour entering the sieve also reacts with nitric oxide to form nitric acid which leads to degeneration of the sieve. Clearly if our bench top experiment is to be applied clinically, all possible precautions must be taken to exclude water from the sieve. We have already alluded to the possible use of a bed of silica gel. Condensation trapping devices could also be used.

We do not believe that any other technical errors are to blame for the large discrepancy between our own observations and those of Findlay, Swart and Smithies. The sieving capabilities of the zeolite depend on its existence in the dehydrated state.

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# BOOK REVIEWS

*Interventional Pain Management.* WALDMAN AND WINNIE (editors). Published by WB Saunders and Co, London. Pp. 582; indexed; illustrated. Price £97.00.

Perhaps the title of this new book does not give justice to its content. The volume is more than an encyclopaedia of practical procedures; it is a comprehensive dissertation on many aspects of chronic pain but with an emphasis on interventional techniques. The editors have assembled contributions from nearly 50 authors, mainly from the USA, and incorporated numerous diagrams and photographs. It consists of six sections: anatomy and physiology of pain, patient evaluation, neural block, neural augmentation, spinal opioids and, finally, neurosurgical techniques.

The first two sections provide useful summaries on the background of pain management A particularly good chapter describes the functional anatomy of the spine. However, the heart of the book is in section 3 where 25 chapters describe various neural blocks. It is clear that the authors of these chapters perform these blocks very regularly as the text is full of practical tips and hints. There are scores of clear radiographs and line diagrams. It is very difficult to find a neural block which is not well described in this section. Although multiple authors have contributed to this section, the chapters follow a set format. Therefore, each block is considered under historical considerations, indications, contraindications, relevant anatomy and practical considerations and complications. The quality of the illustrations cannot be over emphasized

The fourth section considers spinal cord and peripheral nerve stimulation Again, a practical approach to this area is taken but there are also excellent chapters considering the mechanism of action of neural stimulation, selection of patients and problems of the techniques. The fifth section addresses the use of spinal opioids and the first chapter summarizes very nicely the current status of this technique. Again, the emphasis is on practical considerations and the early detection of problems and their management. The final section considers briefly neurosurgical techniques for the management of pain and provides a logical conclusion to the book.

I am sure that all practitioners in chronic pain management will find this book of great practical value. The index of books such as this is very important and I have found it accurate and comprehensive. Although I have emphasized the practical nature of this book, each chapter is supported by numerous references, many very recent.

In summary, this is a significant contribution to the available literature on chronic pain management. If you require a book which comprehensively describes every block you are likely to perform and guides you through procedures step-by-step, then buy this one

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*Psychology of Pain.* S. SKEVINGTON. Published by John Wiley, Bognor Regis. Pp. 348; indexed. Price £16.99.

It was a privilege and pleasure to be asked to review this excellent textbook. Dr Skevington has offered a penetrating and scholarly analysis of the psychology of pain seen from her particular perspective as a social psychologist. The book therefore differs from other books both in its standpoint and also in much of its content.

The introduction sets the emphasis of the book not only as an articulation of socio-cognitive processes, but as an examination of the social context in which communication occurs about pain. Given the clear limitations of the signs and symptoms based approach of traditional medicine, with its associated iatrogenic incapacity, Skevington's book offers an illuminating slant on the treatment process which is particularly relevant in this new era of "evidence-based" medicine.

Chapter 1 on biological mechanisms, and chapter 2 on measuring painful sensations, while covering much material available elsewhere in the literature, form a clear and helpful background for the initiate.

Chapter 3 on learning about pain offers much more than a traditional "learning-theory" analysis of pain behaviour in terms of stimuli and responses. It offers essentially an analysis of how people become pain patients. Although some of the theoretical background to consultation behaviour may be familiar to the more psychologically oriented, the chapter is well referenced and offers a refreshing update to the field, particularly from the viewpoints of development across time and of the family context.

One of the strongest features of the book is the link between beliefs, images and memories of painful illness (chapter 4); beliefs about control and causation (chapter 5) and "taking the decision" (chapter 6). In chapter 4, the development of beliefs about pain in childhood is linked with an analysis of the social processes involved in the development of identity as a pain sufferer. In this process, the role of memory of pain in shaping pain experience is seen as critical. Beliefs about control and causation affecting pain and illness are outlined in chapter 5. The material and analysis in this chapter will be familiar to most readers. The discussion of PCA is particularly interesting.

It is argued in chapter 6 that although the role of cognitive factors in health care seeking has been well recognized in the literature, the mechanisms of health care seeking (from the psychological point of view) have not been adequately explored. The scholarly description of subjective expected utility (SEU) theory, the health belief model (HBM) and the theory of reasoned action (TRA), while critical to an adequate understanding of the decision-making process, are perhaps a little esoteric for the general pain specialist.

Chapter 7, on the consultation process, is much more "accessible". Analysis of distress, suffering and loss leads to discussion of the nature of communication about pain, which is appraised both from the verbal and non-verbal perspectives. The second part of the chapter of health care seeking and doctor–patient communication is particularly interesting. In addition to a wealth of illuminating general analyses, pain relief in children and the treatment of burns are considered as situations in which emotion has a high profile. The chapter concludes with a consideration of sense of the socio-emotional impediments to successful pain relief.

Chapter 8, on coping with pain, contains much that will be familiar to readers of the journal *Pain.* The chapter serves as a useful source for much of the "coping" literature. Attention is drawn, rightly, to some of the conceptual ambiguities still present in this field. The concluding section on how doctors cope with pain offers an interesting perspective.

An analysis of the social features of treating pain is offered in chapter 9. Written from a fairly holistic perspective, cancer pain specifically is investigated. More specific topics such as treatment adherence and the placebo effect are considered. Both are examined from a social perspective. The chapter concludes with a section on alternative therapy, but in fact considers mainly acupuncture and TENS.

In the final chapter (10), the "way forward" is considered. A number of additional topics such as gender, ethics and social policy are considered. These are described as "broader issues", although there is a suspicion that they are examples of "unfinished business", aspects of which have been dealt with throughout the book The issue of quality of life is also addressed. The book concludes with a model of psychosocial processes and social factors in the form of a helpful figure (pp292–293) which depicts the author's overall framework and represents the breadth of canvas on which the author has decided to paint.

In conclusion, this book is an important contribution to the scientific literature. It should certainly be mandatory reading for all psychologists in the field of pain. It is well referenced and as such, in addition to its intrinsic merit, will serve as an invaluable source. It offers a unique and penetrating guide to the psychosocial processes surrounding pain and its interpretation. While the book does not attempt to appraise, except in passing, the worth of clinical intervention, it is perhaps a pity that more attention was not paid to the social psychology of the modern interdisciplinary pain management programmes currently being developed not only as tertiary treatment facilities, but also in primary care and occupational settings. However, the strengths of the book are considerable, and there is much of value for all professionals in the field of pain.

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*"I would have everie man write what he knowes and no more."*—MONTAIGNE

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## EDITORIAL I

### Recovery after major surgery: does the anaesthetic make any difference?

Recovery is a term used frequently in anaesthetic and surgical publications. Many factors may affect recovery, but what does the term imply? Among doctors, nurses and patients the term may be perceived very differently. An anaesthetist may state that recovery has occurred when the patient regains consciousness and physiological stability is present; a surgeon may claim that the patient has recovered when the sutures are removed or when the patient is discharged from hospital. Patients, however, may consider that recovery only ensues when they are able to return to work or have the energy to resume their previous lifestyle. With so many different interpretations, patient recovery becomes extremely difficult to measure.

The variable used most often to assess recovery is duration of hospital stay. It is a reasonable assumption that the patient must have gained some degree of recovery to leave hospital, but this variable is influenced by many factors. For example, the practice of keeping patients in hospital so that they can vacate beds as the next surgical patient arrives, artificially prolongs duration of stay. Despite the absence of accurate data, it is important to consider if modern anaesthetic and surgical practices have hastened recovery after major surgery.

Duration of hospital stay has been declining over the past four decades, not only in the National Health Service (NHS), but also in the private sector.[1] Patients undergoing hysterectomy in the NHS between 1948 and 1957 stayed in hospital for 21 days, but this had decreased to 10 days by 1978–1983. This trend has also been noted in the USA, in spite of an increase in the complexity of medical problems associated with surgery.[2] Duration of stay continues to decrease, and in our hospital in London in 1996, patients undergoing hysterectomy stayed for only 4–5 days. Two key facets of anaesthesia may be implicated; attenuation of the neuroendocrine response to surgery and improved analgesic regimens.

Following Kehlet's suggestion that neuroendocrine changes are not essential and obtunding them may improve surgical outcome, extradural analgesia and anaesthesia have been used extensively to decrease the stress response to surgery. Occasional reports have found beneficial effects on morbidity, and even mortality,[3–5] but two comprehensive reviews in 1988 and 1995 found only limited improvements in selected surgical procedures.[6,7] Indeed, Liu, Carpenter and Neal concluded that more studies are needed to determine if a relationship exists between the stress response and postoperative morbidity.[7] Few investigators have examined the problem directly and most data are derived from studies in which recovery was not a primary end-point. Liu, Carpenter and Neal also argue for more and better variables to assess recovery, such as return to work.

An improvement in postoperative analgesia has become the major thrust of many anaesthetic departments in recent years. Patient-controlled analgesia (PCA) has been adopted enthusiastically and there have been many studies promoting its advantages over conventional analgesic regimens. Although there were a few early reports indicating a more rapid discharge from hospital with PCA, meta-analysis of initial, randomized, control studies found no significant improvement.[8] Mean duration of hospital stay was only 0.15 days shorter with PCA compared with conventional regimens. Neural block provides excellent postoperative pain relief, but again has little impact on recovery. Two studies using extradural analgesia after orthopaedic and colonic surgery failed to show a decrease in the duration of hospital stay.[9,10] The effects of different extradural analgesic regimens on recovery after colonic surgery were reported recently.[11] Extradural bupivacaine and extradural bupivacaine–morphine provided better analgesia than extradural morphine or morphine PCA, and were associated with more rapid recovery of gastrointestinal function. However, duration of hospital stay was similar in all groups, although the time to fulfil predetermined discharge criteria was improved significantly in patients who received extradural bupivacaine or extradural bupivacaine–morphine. The authors emphasized that, despite prospective agreement with all surgeons, and education of patients, nurses and residents, some patients were not discharged on meeting the fixed criteria. Reasons included travel arrangements, social situations and the patient's or surgeon's belief that further observation in hospital was necessary. This study encapsulates the difficulties in trying to examine the effects of anaesthetic techniques on recovery.

It seems likely that anaesthesia has only a minor role to play in enhancing recovery. Changes in surgical technique and the introduction of laparoscopic procedures have been more productive. There is general agreement that duration of hospital stay is much less when cholecystectomy is conducted laparoscopically than by laparotomy.[12,13] Similar benefits have been claimed for appendicectomy,[14] and laparoscopic hernia repair was associated with more rapid return to work.[15] The consensus on the benefits of laparoscopic cholecystectomy was challenged in 1996 when a laparoscopic technique was compared with small-incision laparotomy[16]; there was no difference in duration of hospital stay, time back to full employment and time taken to return to full activity. This study used a novel method of determining recovery; the patient decided when to leave hospital. It is of interest that the duration of stay was 3 days with both techniques, possibly longer than anticipated after laparoscopy and shorter than expected after mini-laparotomy.

Nevertheless, the use of laparoscopic techniques is associated with rapid recovery and early discharge. The classical neuroendocrine response to abdominal surgery is similar with both techniques, but there is a significant decrease in markers of the inflammatory response to tissue damage, such as interleukin-6 and C-reactive protein with laparoscopy.[17 18] The concept that tissue damage is a key determinant of recovery is supported by studies in which the length of the abdominal incision was varied[19] and the use of even smaller laparoscopic ports.[20]

Bardram and colleagues combined recent developments in surgical and anaesthetic practice to enhance recovery in nine elderly patients undergoing colonic surgery.[21] The surgery was laparoscopically assisted and this was combined with extradural analgesia with bupivacaine, early oral feeding and rapid mobilization. Opioids were avoided, if possible, and used only for rescue analgesia. Hospital stay was decreased to 2–3 days compared with the usual 8–10 days. These results are extremely impressive and show what can be achieved by enthusiastic anaesthetic and surgical collaboration. It is not possible from the design of the study to identify those factors responsible for the improvement. Further work with larger numbers of patients and suitable control groups will permit the relative contributions of anaesthetic and surgical factors to be determined.

At present we anticipate that patients who undergo major surgery will stay in hospital for up to 10 days. These expectations are known widely in the community and in hospital. Majeed and colleagues found it necessary to blind the nursing staff and the patient to the type of surgery (laparoscopy or mini-laparotomy for cholecystectomy).[16] This was achieved by randomizing patients after they had been anaesthetized, restricting nursing access to the operative details and by placing identical blood stained dressings on the patients. The dressings were not removed until the patient decided that they were fit for discharge. The investigators also wrote to the general practitioners asking them not to influence the time taken by the patient before returning to work. The care taken to try to eliminate bias in this study shows how entrenched the expectations of patients, doctors and nursing staff are over recovery from major surgery. Cultural factors may be as important as anaesthetic and surgical techniques in influencing recovery.

Research into recovery after surgery is important for information, planning and economic reasons. A clear definition of recovery must be found together with an effective method of measuring this variable. We have discussed briefly some of the problems associated with using duration of stay to assess recovery. The patient's view of recovery must be taken into account and not just those areas of interest to medical staff (resumption of oral intake, days of analgesic therapy, etc). This requires research projects to be extended into the period of convalescence after the patient has left hospital. This critical time has largely been ignored, so far, and yet is of major importance to the patient.

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# EDITORIAL II

## Low-dose dopamine: will there ever be a scientific rationale?

Perioperative renal dysfunction is a well recognized complication in patients undergoing elective repair of abdominal aortic aneurysm (AAA). Postulated mechanisms include diminished preoperative renal function, tubular functional impairment secondary to altered intrarenal circulation, activation of the renin–angiotensin–aldosterone system, reduced distal tubular sodium delivery and atheromatous emboli.[1 2] Infrarenal aortic cross-clamping *per se* has been demonstrated to produce profound and sustained alterations in renal haemodynamics (38% reduction in renal blood flow and 75% increase in renal vascular resistance) in the absence of significant changes in cardiac output or systemic vascular resistance.[3] Prolonged aortic cross-clamping, hypotension and large-volume blood transfusion are important risk factors in the development of postoperative renal impairment in this patient population.[4] Acute renal failure (ARF) in this context carries a high mortality rate, and its avoidance is an important goal of postoperative management.[5] Hence, the findings of Girbes and colleagues[6] in a recent issue of *British Journal of Anaesthesia* that an infusion of dopamine 2–4 $\mu g\ kg^{-1}\ min^{-1}$ increased glomerular filtration rate (GFR) and renal blood flow (RBF) in seven haemodynamically stable patients undergoing mechanical ventilation and receiving postoperative extradural analgesia after elective AAA repair merits attention and critical analysis. The authors attributed the dopamine-induced increased GFR and RBF to increased cardiac output and they went on to conclude that "if an increase in RBF and GFR is considered as a goal of treatment, our data indicate that 4 $\mu g\ kg^{-1}$ is the optimal dose of the given doses".

Do the findings of this study support the claims often made by proponents of "renal-dose" or "low-dose" dopamine that such a regimen augments RBF, GFR and/or natriuresis in healthy humans and experimental animals, and limits adenosine triphosphate utilization and oxygen requirements in nephron segments at risk for ischaemic injury, actions that could potentially limit renal injury and accelerate recovery in ARF?. Undoubtedly, dopamine infusion induces a dose-dependent increase in RBF, natriuresis and diuresis in healthy experimental animals and humans[7] and improves RBF in patients with chronic renal impairment, renovascular disease and mild to moderate sodium depletion.[8] The mechanisms by which dopamine modulates RBF differ depending on the rate of infusion.[9] At low doses (threshold 0.5, maximum 3.0 $\mu g\ kg^{-1}\ min^{-1}$), dopamine augments RBF principally by DA1 receptor-induced intrarenal vasodilatation and possible contributory engagement of DA2 receptors on presynaptic sympathetic nerve terminals with inhibition of noradrenaline release. Intermediate doses of dopamine (threshold 3.0, maximum 10 $\mu g\ kg^{-1}\ min^{-1}$) are thought to augment renal perfusion by increasing cardiac index via cardiac $\beta_1$-adrenoreceptor stimulation. Higher doses of dopamine administration (threshold 5.0, maximum 20 $\mu g\ kg^{-1}\ min^{-1}$) may produce systemic vasoconstriction via $\alpha$- adrenoceptor stimulation.

An important caveat worthy of note is that the above-mentioned dopamine dose–response relationships were advanced after studies in normovolaemic healthy subjects. Do they apply to the potentially hypovolaemic and hypothermic patient, with coexisting ischaemic heart disease, hypertension or diabetes in the immediate postoperative period? In this uncontrolled, small scale study of relatively normovolaemic, normothermic patients without coexisting cardiac or renal impairment, infusion of dopamine 2–4 $\mu g\ kg^{-1}\ min^{-1}$ increased urine output, GFR and RBF. What was/were the mechanism(s) involved?. The mechanisms by which dopamine exerts its renal effects are complex and might include: $\beta$-adrenoceptor-mediated increase in cardiac output; DA1 and DA2 receptor-mediated vasodilatation and increased RBF; increased delivery of diuretics to the distal tubule; decreased renin–angiotensin–aldosterone activation; or direct effects on tubular function.[10] Increased cardiac output and RBF were the most striking findings in the study by Girbes and colleagues.[6] Plasma renin activity was essentially unchanged, while plasma aldosterone concentrations were reduced significantly when an infusion of dopamine 8 $\mu g\ kg^{-1}\ min^{-1}$ was given. Dick, Dasta and Choban, in a study of oliguric, critically ill surgical patients, reported that an infusion of dopamine 2–5 $\mu g\ kg^{-1}\ min^{-1}$ for 6 h decreased serum aldosterone concentration with increased urine output and sodium excretion.[11]

Do the results of this study suggest a role for prophylactic low-dose dopamine in this clinical context? The authors make no such claim based on their observations. Moreover, several recent editorials have strenuously urged abandonment of low-dose dopamine therapy in the treatment of ARF.[10 12] Paul and colleagues observed no clinically important benefit from intraoperative administration of mannitol and dopamine compared with extracellular fluid volume expansion with saline alone in the prevention of changes in renal function associated with aortic cross-clamping.[13] Studies assessing the efficacy of "renal" or low-dose dopamine in the prevention of ARF in high-risk clinical situations—major cardiac surgery, vascular or biliary surgery, renal and liver transplantation, and exposure to contrast material—have been challenged on the basis of patient numbers and study methods. In a prospective, randomized controlled study of 37 patients undergoing elective abdominal aortic surgery, 24-h infusion of dopamine 3 $\mu g\ kg^{-1}\ min^{-1}$ in the postoperative period did not improve creatinine clearance or reduce serum creatinine concentrations measured after 1 and 5 days, respectively.[14] Two postoperative deaths occurred in the dopamine group (from renal failure and myocardial infarction). Four patients had myocardial infarction, three of whom received dopamine.

In examining the potential therapeutic effects of low-dose dopamine, it is necessary to perform a risk–benefit analysis regarding deleterious side effects.[15] This process is essential when the treatment is of questionable benefit. Girbes and colleagues[6] reported no major changes in heart rate in the seven patients studied. None the less, dopamine is a potent catecholamine, with positive inotropic and chronotropic activity, even in the low doses used in the study. Apart from the obvious potential problems with tachycardia and increased myocardial oxygen consumption, dopamine may depress hypoxic respiratory drive[10] and, in a porcine shock model, was reported to divert blood flow away from the gut mucosa.[16] Administration of dopamine warrants central venous cannulation, and drug extravasation adjacent to an artery may provoke distal ischaemia and gangrene.[17]

There is no doubt that dopamine in low doses in healthy kidneys leads to an increase in urine output, accompanied by natriuresis and kaliuresis. Low-dose dopamine, as used by Girebes and colleagues,[6] appeared to function as a "diuretic" with perhaps some inotropic and renal vasodilator properties. This diuresis would be a dubious blessing if it were to mask or even cause hypovolaemia and subsequent renal hypoperfusion. The absence of prospective, controlled, large-scale studies confirming reduced incidence of ARF and improved outcome three decades after the first reports of administration of renal protective doses of dopamine remains a concern. Perhaps clinicians and investigators should focus attention on catecholamines such as dobutamine, devoid of diuretic properties, but with the potential to augment cardiac output and renal blood flow?

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CLINICAL INVESTIGATIONS

# Effect of an upper respiratory tract infection on upper airway reactivity

N. NANDWANI, J. H. RAPHAEL AND J. A. LANGTON

## Summary

Patients presenting for elective anaesthesia and surgery may be suffering with, or recovering from, a recent upper respiratory tract infection (URTI). It is a frequent clinical problem as to whether to postpone surgery in such patients as they may be more likely to suffer adverse respiratory events related to administration of general anaesthesia. Using dilute ammonia vapour as a chemical stimulus, we measured upper airway reactivity in 11 healthy volunteers (six males), mean age 39.8 (range 30–58) yr, who had symptoms of an URTI. Volunteers were recruited 24–72 h after symptoms first began, and followed-up at regular intervals for the next 8 weeks. Measurements of upper airway reactivity were made on the following days (±24 h) after commencement of URTI symptoms: 3, 6, 9, 15, 20 and 27. Additional measurements were obtained 56 days after symptoms first began, and these were regarded as baseline measurements. Upper airway reactivity was increased on days 3, 6 and 9 compared with baseline measurements ($P<0.01$, Wilcoxon). There was no significant change in airway reactivity from day 15 onwards, by which time 10 of the 11 subjects were completely devoid of symptoms. All subjects were asymptomatic by day 20 and remained so until the study ended on day 56. We conclude that upper airway reactivity was increased during the acute phase of an URTI, and that this appeared to be related to the presence of symptoms. (*Br. J. Anaesth.* 1997; **78**: 352–355).

**Key words**
Airway, reflexes. Infection, respiratory tract. Complications, respiratory. Complications, infection.

Most adults suffer at least one upper respiratory tract infection (URTI) per year. The incidence increases to 5–6 episodes per year in children. Therefore, many patients presenting for elective surgery and anaesthesia may either be suffering with, or recovering from, a recent URTI.

The decision whether or not to anaesthetize such a patient is a common clinical dilemma. In the past it has been routine practice to postpone anaesthesia and surgery in patients suffering from an URTI, but this may have medical, social and financial consequences. There have been relatively few studies investigating this important clinical area and these have focused on the incidence of adverse respiratory events associated with anaesthesia in children. In a large prospective study, Cohen and Cameron studied 1283 children with symptoms of an URTI and 20 876 children without any symptoms who were undergoing elective surgery.[1] They found that children suffering from an URTI were three times more likely to suffer an adverse respiratory event; the risk increased 11-fold if tracheal intubation was performed. In 1992, Levy and colleagues[2] found that children with an acute or recent URTI had an increased likelihood of transient hypoxaemia in the perioperative period. There has also been a well documented case report of laryngospasm resulting in death in a child recovering from a recent URTI.[3] It has even been suggested that an anaesthetist may be negligent for anaesthetizing a child while suffering from an URTI.[4]

At present there are few studies which have investigated adult patients with symptoms of an URTI undergoing anaesthesia. There is however evidence of increased bronchial reactivity in adults suffering from an URTI; Empey and co-workers demonstrated a 200% increase in airway resistance in response to inhaled histamine in subjects with colds compared with a 30% increase in controls.[5] There is however little evidence to demonstrate that anaesthesia in adult patients with an URTI leads to an increased incidence of respiratory complications.

We are able to measure upper airway reactivity in subjects by using dilute ammonia vapour as a chemical stimulus to the upper airway.[6] The aim of this study was to determine the sensitivity of upper airway reflexes during an URTI and to record the duration of any possible changes and the relationship of these changes to the presence of symptoms.

## Subjects and methods

After obtaining Ethics Committee approval and written informed consent, we studied 12 volunteers,

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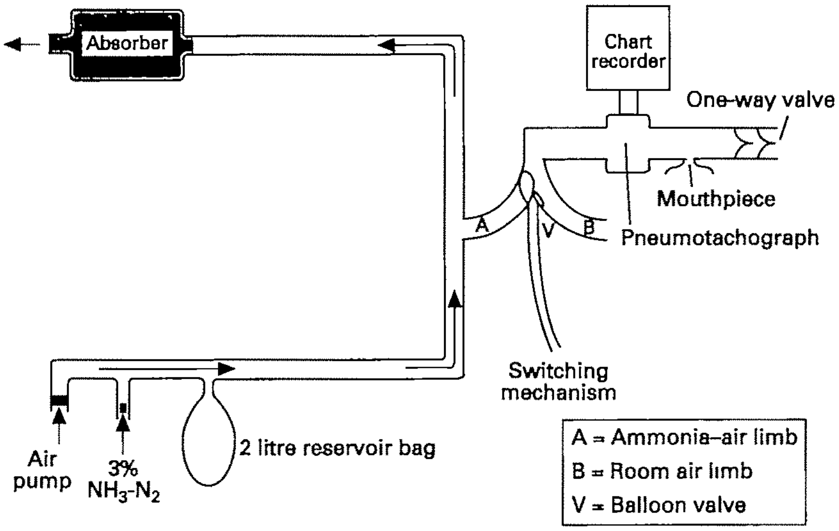

*Figure 1* Schematic diagram of the equipment used to measure upper airway reactivity.

24–72 h after symptoms of an URTI first began. All volunteers were non-smokers and not receiving any medication. Exclusion criteria included a history of asthma or an URTI in the previous 3 months.

URTI was defined according to similar criteria as used by Tait and Knight.[7] Symptoms were divided into three categories: nasal—discharge, obstruction, sneeze; throat—sore throat, non-productive cough; systemic—malaise, muscular ache, temperature less than 38 °C.

Subjects were recruited into the study if they had at least one symptom from each category and were deemed to be asymptomatic only when all symptoms had completely disappeared. Subjects were not studied if they had a temperature greater than 38 °C, productive cough or evidence of lower respiratory tract infection.

All subjects were followed-up at regular intervals over the next 8 weeks. Measurements of upper airway reactivity were made on the following days (±24 h) after commencement of URTI symptoms: 3, 6, 9, 15, 20 and 27. Additional measurements were obtained 56 days after symptoms first began and these were regarded as baseline measurements. The presence or absence of symptoms was also recorded.

Upper airway reflex sensitivity was measured using a previously described method which uses low concentrations of ammonia vapour as an irritant chemical stimulus to the upper airway during inspiration.[6] Briefly, the subject was asked to breathe through a close-fitting mouthpiece while wearing a noseclip and to exhale to atmosphere via a one-way valve (fig. 1). The mouthpiece was attached to a pneumotachograph which records airflow onto a chart recorder. A pneumatic two-way balloon valve was situated between limbs A and B of the breathing circuit. This balloon valve allowed the investigator to switch rapidly between room air and dilute ammonia vapour. Subjects wore dark goggles and listened to music through headphones so that they were unaware of the switching of the pneumatic valve.

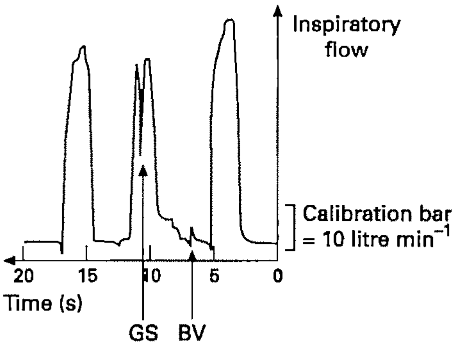

*Figure 2* Example of a glottic stop recording. GS=Glottic stop, BV=switching of the balloon valve, allowing the subject to take a single breath from the ammonia–air limb.

In this way the subject's upper airway was exposed to single intermittent breaths containing small concentrations of ammonia vapour and the threshold concentration ($NH_3TR$) required to elicit glottic closure was recorded. We defined glottic closure as a rapid decrease in inspiratory flow, the flow decreasing by at least 25% of peak inspiratory flow, followed by a swift recovery, and the whole event lasting less than 0.5 s (fig. 2). Low values for $NH_3TR$ are associated with increased sensitivity of the upper airway, high values represent depression of upper airway reflex sensitivity.

Ammonia was supplied via a Rotameter from a 3% ammonia–nitrogen cylinder supplied by the British Oxygen Company. This was added to room air 10 litre $min^{-1}$ to deliver accurate concentrations of ammonia vapour in the range 0–3500 ppm. Calibration of the system has been described previously.[6] By altering the flowmeter settings by increments of 50 ml $min^{-1}$, corresponding to mean (range) changes in ammonia concentration of 171 (125–235) ppm, we were able to determine the minimum concentration of ammonia vapour required to elicit glottic closure ($NH_3TR$).

## Results

Eleven subjects (six males), mean age 39.8 (range 30–58) yr, completed the study. One subject was completely devoid of symptoms by day 6, five by day

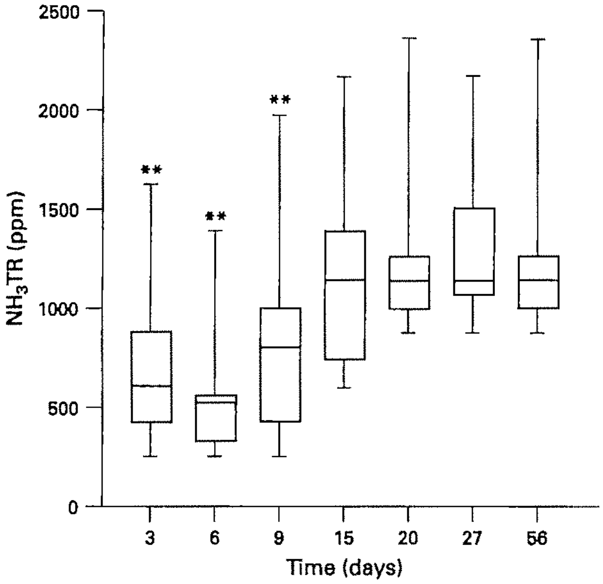

*Figure 3* Ammonia threshold concentration ($NH_3TR$) in volunteers with an upper respiratory tract infection (URTI) showing the median, interquartile range and 10th and 90th percentiles. **$P<0.01$ (Wilcoxon).

9 and 10 by day 15. All were asymptomatic by day 20 and remained so until the study ended on day 56 when the baseline $NH_3TR$ measurements were recorded.

There was a decrease in $NH_3TR$, corresponding to an increase in upper airway reactivity, from a baseline mean of 1255 (SEM 126) ppm to 674 ppm (116) on day 3, 587 ppm (108) on day 6 and to 806 ppm (170) on day 9 after the commencement of URTI symptoms (fig. 3). Using Friedman two-way ANOVA and Wilcoxon matched pairs signed ranks test, these changes were statistically significant ($P<0.01$).There was no significant change in $NH_3TR$ compared with baseline measurements from day 15 onwards.

## Discussion

Upper airway reflex activity is important to the anaesthetist because it is involved in both airway protection and upper airway complications such as cough and laryngospasm. We are able to measure upper airway reactivity using small concentrations of ammonia vapour as a chemical stimulus to the upper airway.[6] Using this technique previous studies have shown that airway reflexes are depressed by administration of oral benzodiazepines[8] and also by topical administration of lignocaine to the vocal cords.[9] It has also been shown that upper airway reactivity decreases with advancing age.[10] In comparison, chronic smokers have significantly greater airway reactivity than non-smokers,[11] an effect that can last for up to 10 days after abstinence from cigarettes.

The exact mechanism responsible for reflex glottic closure has not been fully elucidated. Receptors known to respond to chemical irritants are found in the epithelial and subepithelial layers of the pharynx and larynx. Afferents from these receptors travel mainly in the superior laryngeal nerve and synapse in the brain stem. In adult humans the main response to irritant receptor stimulation is glottic closure and a brief pause in inspiration. Higher concentrations of irritants result in cough. We have used the threshold concentration of dilute ammonia vapour required to elicit glottic closure ($NH_3TR$) as a measure of upper airway reactivity.

It is thought that the epithelial lining of the upper airway plays an important role in restricting access of inhaled irritants to the subepithelial receptors. It is known that infection of the upper respiratory tract results in mucosal oedema followed by shedding of the epithelial cell layers.[12] Loss of airway epithelium can extend down to the basement membrane and may persist for as long as 3 weeks after the initial infection. Our findings of increased upper airway reactivity during the acute phase of an URTI agree with the findings of Empey and colleagues, who demonstrated that bronchial reactivity in response to inhaled histamine is increased during an URTI.[5] Chronic smokers also develop inflammation and destruction of the protective epithelial barrier[13] and this may account for the increase in upper airway reactivity which has been demonstrated previously.[11]

The diagnosis of URTI is complicated by the fact that a particular clinical syndrome is not always associated with a specific pathogen. The rhinovirus, myxovirus and respiratory syncytial virus are the most common pathogens. We recruited subjects on the basis of the presence of symptoms attributable to an acute URTI.[7] We did not attempt to perform viral cultures as this would have been neither practical nor cost-effective for a self-limiting usually benign condition. In everyday anaesthetic practice the presence of symptoms would be used to assess the need to postpone surgery.

There is some interest in the effect of inhaled anaesthetic agents on the course of an URTI. It has been suggested that after surgery and anaesthesia there may be a decrease in both the severity and duration of certain respiratory symptoms. Tait and Knight[7] found a significantly lower incidence of sore throat, sneezing, malaise and fever in children after general anaesthesia compared with those that were not. Earlier *in vitro* studies examining exposure of several viruses to halothane demonstrated dose-dependant inhibition of viral replication.[14] This effect is thought to result in part from a decrease in synthesis of viral proteins, although these *in vitro* experiments required an exposure time equal to the replicative time of the virus. Nevertheless these studies demonstrate the sensitivity of some viruses to anaesthetic agents which could potentially be reflected in the clinical situation. These findings are of special interest as they add an additional clinical perspective.

An editorial in the *British Journal of Anaesthesia* in 1990[15] highlighted the fact that to date there is little evidence to show that general anaesthesia administered to an adult patient with an URTI results in an increased incidence of adverse respiratory events. Our study has demonstrated that upper airway reactivity was increased during the acute phase of an URTI. In addition, we have shown that this increase appeared to be related to the presence of symptoms. However, the exact relationship between an increase in the sensitivity of airway reflexes and the incidence of upper airway problems requires further investigation.

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# Inhalation induction with sevoflurane: a double-blind comparison with propofol†

A. THWAITES, S. EDMENDS AND I. SMITH

## Summary

We conducted a randomized, double-blind comparison of 8% sevoflurane and propofol as induction agents for day-case cystoscopy in 102 patients. All patients received an i.v. cannula and breathed oxygen 5 litre min$^{-1}$. Anaesthesia was induced with propofol i.v. or inhalation of 8% sevoflurane and 10% Intralipid (as a placebo) i.v., delivered by a blinded observer. Anaesthesia was maintained in all patients with 2% sevoflurane via a face mask. Induction of anaesthesia with sevoflurane was significantly slower compared with propofol (mean 84 (SD 24) s *vs* 57 (11) s), but was associated with a lower incidence of apnoea (16% *vs* 65%) and a shorter time to establish spontaneous ventilation (94 (34) s *vs* 126 (79) s). Induction complications were uncommon in each group but the transition to maintenance was smoother with sevoflurane and was associated with less hypotension compared with propofol. Emergence from anaesthesia induced with sevoflurane occurred significantly earlier compared with propofol (5.2 (2.2) min *vs* 7.0 (3.2) min) and anaesthetic induction was also significantly cheaper with sevoflurane. According to a postoperative questionnaire, the majority of patients found both anaesthetic techniques acceptable. Nevertheless, significantly more patients (14%) rated induction with sevoflurane as unpleasant compared with propofol (0) and significantly more patients (24%) would not choose sevoflurane induction compared with propofol (6%). This phenomenon may have been related to the particular patient population studied, however. Inhalation induction with 8% sevoflurane would appear to offer several objective advantages compared with induction with propofol in day-case patients, although a significant minority may dislike this technique. (*Br. J. Anaesth.* 1997; **78**: 356–361).

**Key words**
Anaesthetics volatile, sevoflurane. Anaesthetics i.v., propofol. Anaesthesia, day case. Anaesthetic techniques, induction.

One of the major objections to performing inhalation induction of anaesthesia is patients' dislike of a black rubber face mask. Nevertheless, the widespread availability of modern clear plastic masks, combined with an increasing tendency to use face masks to perform "preoxygenation" before induction of anaesthesia have largely overcome this objection. With the availability of a non-pungent and rapidly acting volatile anaesthetic, it would seem logical to use a face mask both to provide oxygen and induce anaesthesia, thereby avoiding many of the problems associated with i.v. induction.

Sevoflurane has a low blood:gas solubility coefficient (0.69)[1] and is the least respiratory irritant of the available volatile anaesthetics.[2] These properties make sevoflurane an ideal inhalation induction agent.[3] Previous investigations have shown sevoflurane to be an acceptable induction agent in adult patients.[4 5] However, these investigators used an earlier sevoflurane vaporizer which was limited to a maximum output of 5% (compared with 8% on current models). In addition, patients were pretreated with opioid analgesics. Finally, the earlier comparisons were not blinded and did not specifically examine the patient's experience of induction. We therefore conducted a randomized, double-blind comparison of induction of anaesthesia in unpremedicated patients with 8% sevoflurane or propofol (the most commonly used induction agent).

## Patients and methods

We studied 102 ASA I–III patients undergoing day-case cystoscopy for follow-up of bladder carcinoma, haematuria or urinary tract infection, according to a design approved by the Ethics Committee of the North Staffordshire Hospital. After obtaining written, informed consent, patients were allocated randomly to one of two induction groups using computer-generated random numbers and sequentially numbered sealed envelopes. All patients were unpremedicated. Patients with a previous history of malignant hyperthermia or adverse reaction to inhalation anaesthetics or propofol were excluded. Patients receiving sedative medications chronically

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and those with serious, life-threatening respiratory or cardiovascular diseases were also excluded.

Before induction of anaesthesia, one anaesthetist (A. T.) prepared a 20-ml syringe containing either propofol or 10% Intralipid as a placebo control. A 20-gauge i.v. cannula was inserted into the patient's non-dominant hand and 2 ml of 1% lignocaine were administered to all patients. Although lignocaine was injected as prophylaxis against pain on injection of propofol, it was administered to both groups of patients because of possible effects on haemodynamic variables. All patients received oxygen for 1 min from a clear plastic face mask at a flow rate of 5 litre $min^{-1}$ and patients were given a weighted object to hold.[6] At the start of induction of anaesthesia, fresh gas flow was changed to nitrous oxide 4 litre $min^{-1}$ and oxygen 2 litre $min^{-1}$ in all patients. In the sevoflurane group, the non-blinded anaesthetist (A. T.) turned the sevoflurane vaporizer to 8% at the start of induction. A similar hand movement was made in the propofol group, but the vaporizer dial was not actually turned. The sevoflurane vaporizer was hidden from view of the blinded observer (I. S.) by an opaque curtain. Simultaneous with the start of induction, the observer began to inject the contents of the 20-ml syringe (propofol or placebo) at a constant rate of 16–18 ml $min^{-1}$ and continued until the patient dropped the weighted object. Spontaneous patient activities and comments were recorded by the observer. Arterial pressure, heart rate and haemoglobin oxygen saturation ($Sp_{O_2}$) were recorded at 1-min intervals during induction. The observer judged anaesthesia to be induced when the patient dropped the weighted object. At this point, the volume of i.v. drug injected was recorded and anaesthesia was maintained with 2% sevoflurane in both groups of patients, subsequently adjusted up or down as necessary in order to maintain adequate anaesthesia as judged by the usual clinical signs.[7] Anaesthesia was maintained using a face mask. The observer recorded a guess as to which induction agent had been used, evaluated the occurrence of apnoea and recorded when spontaneous ventilation resumed. The occurrence of movements and coughing during the transition period from induction to maintenance was also recorded. All induction sequence events were timed using a palm top computer (Psion, London) and custom software. Oxygen and anaesthesia were delivered using a Humphrey ADE circuit used in its "A" setting. The system was flushed with oxygen 50 litre $min^{-1}$ between patients until the investigators were unable to smell residual sevoflurane.

The costs of induction (see appendix) were calculated on the current list price of the primary induction drug. Induction costs for sevoflurane were based on the list price of the anaesthetic liquid, the volume of vapour produced per ml of liquid (182.7 ml),[8] fresh gas flow and induction time. At the end of the procedure, sevoflurane and nitrous oxide were discontinued simultaneously and the time at which patients opened their eyes to command was recorded by the observer. Before discharge from the day-case unit, patients completed a questionnaire to evaluate their induction experience. Patients were asked about their recollection of the face mask, smells and tastes during induction of anaesthesia and whether or not these were unpleasant. Patients were also asked about pain on injection of the i.v. drug and were asked to guess if their anaesthesia had been induced by "an injection" or by "breathing a gas". Induction of anaesthesia was rated as "pleasant", "neither pleasant nor unpleasant" or "unpleasant". Finally, the patient's willingness to receive an identical anaesthetic induction in the future was determined.

Data were analysed using the Statview statistical package. Continuous variables were analysed using non-paired *t* tests. Discrete data were analysed using chi-square tests or Fisher's exact test as appropriate. Data which were not distributed normally were analysed using an appropriate non-parametric test. In all cases $P<0.05$ was considered significant.

## Results

The two induction groups were comparable in patient characteristics (table 1). Induction of anaesthesia with propofol was significantly more rapid compared with 8% sevoflurane (mean 57 (SD 11) s *vs* 84 (24) s, $P<0.01$). Induction of anaesthesia with propofol required an average of 167 (31) mg (2.3 (0.5) mg $kg^{-1}$). Six patients spoke with slurred speech during induction with propofol compared with seven who received sevoflurane. Purposeful movements were made by three patients in the propofol group and by five in the sevoflurane group ($P=0.46$). In addition, one patient in the sevoflurane group exhibited mild coughing. The induction sequences were sufficiently similar that the observer could identify the induction technique correctly only 65% of the time with propofol and 61% of the time with sevoflurane. Apnoea occurred significantly more frequently in the propofol induction group (33 (65%)) compared with the sevoflurane group (eight (16%)) ($P<0.01$). As a consequence, the time from beginning induction until patients were breathing spontaneously with a regular ventilatory pattern was significantly shorter with sevoflurane compared with propofol (94 (34) s *vs* 126 (79) s, respectively). Coughing after induction of anaesthesia, during the transition to the maintenance phase, occurred in four patients (8%) in the sevoflurane group and in 12 patients (24%) in the propofol group ($P=0.03$).

Mean arterial pressure (MAP) recorded immediately before induction of anaesthesia did not differ significantly between the two groups (fig. 1).

*Table 1* Patient characteristics in the two anaesthetic induction groups. Values are mean (SD or range) or number of occurrences

| | Propofol | Sevoflurane |
|---|---|---|
| Number (*n*) | 51 | 51 |
| Age (yr) | 58 (20–81) | 60 (18–85) |
| Weight (kg) | 73 (14) | 73 (13) |
| ASA (I/II/III) | 18/32/1 | 23/26/2 |
| Sex (M/F) | 29/22 | 31/20 |
| Smoking history | | |
| Non-smoker | 24 | 23 |
| Ex-smoker | 13 | 13 |
| Current smoker | 14 | 15 |

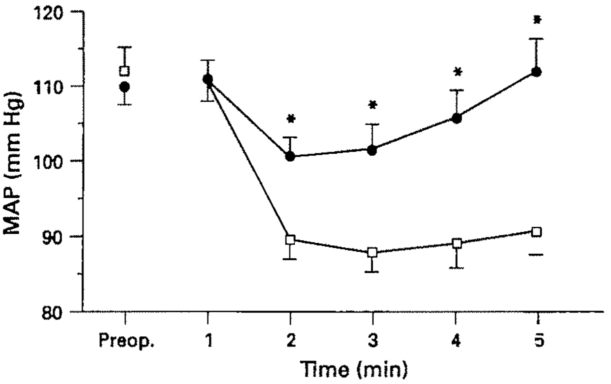

*Figure 1* Mean arterial pressure (MAP) before induction of anaesthesia (Preop.) and at the indicated times after induction of anaesthesia with propofol (□) or 8% sevoflurane (●). Values are mean, SEM. $^*P<0.05$ compared with propofol.

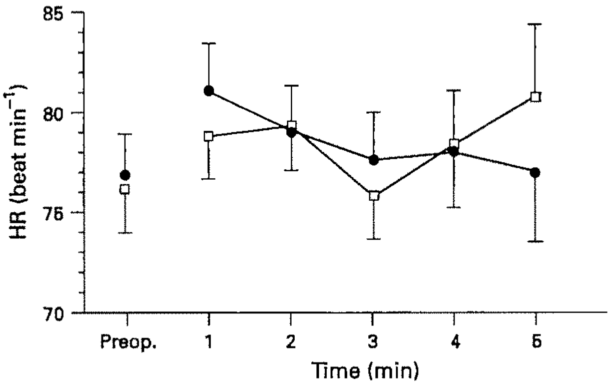

*Figure 2* Heart rate (HR) before induction of anaesthesia (Preop.) and at the indicated times after induction of anaesthesia with propofol (□) or 8% sevoflurane (●). Values are mean, SEM.

Induction of anaesthesia with propofol was associated with a decrease of approximately 20 mm Hg in MAP which occurred within 2 min and persisted for at least the first 5 min of anaesthesia. In contrast, the decrease in MAP with sevoflurane was only 10 mm Hg and MAP had returned to baseline values within 5 min. As a consequence, MAP was significantly lower at 2–5 min after induction of anaesthesia with propofol compared with sevoflurane (fig. 1). Heart rate (HR) increased slightly compared with baseline after induction of anaesthesia with each agent. However, HR did not differ significantly between the groups at any time during induction (fig. 2). There was also no difference in $Sp_{O_2}$ between the two groups at any time.

Patient responses to the postoperative questionnaire are shown in table 2. Most patients recalled the presence of the face mask. While this was well tolerated by the majority of patients, significantly more patients in the sevoflurane group found the face mask unpleasant. Although a smell was reported most commonly by patients receiving sevoflurane (92%), 61% of patients recalled a smell in the propofol group. However, this smell was reported as "unpleasant" by significantly more patients in the sevoflurane group. A taste was also reported more commonly with sevoflurane, although there was no significant difference in the number of patients who described this as unpleasant. When patients attempted to guess which induction technique they had received, they were more inclined to choose the inhalation technique. As a result, significantly more patients guessed correctly in the sevoflurane induction group and incorrectly in the propofol induction group. Induction with propofol was rated as "pleasant" significantly more frequently compared with sevoflurane, with most of the remaining patients either having no recall of induction or providing an indifferent response (neither pleasant nor unpleasant). Induction was described as "unpleasant" by a minority of patients (seven (14%)) all of whom were in the sevoflurane group. There was a tendency for more patients receiving propofol to favour the same induction technique in the future, although this difference was not statistically significant. However, significantly more patients who received sevoflurane (24% *vs* 6%) were unwilling to receive the same induction again ($P=0.02$).

*Table 2* Patient's perspective on induction of anaesthesia. Values are number (%) of responses. $^*P<0.05$ compared with propofol

| | Propofol | Sevoflurane |
|---|---|---|
| Recall face mask | 51 (100%) | 50 (98%) |
| Mask unpleasant | 2 (4%) | 10 (20%)* |
| Recall smell | 31 (61%) | 47 (92%)* |
| Smell unpleasant | 4 (8%) | 15 (29%)* |
| Recall taste | 14 (27%) | 26 (51%)* |
| Taste unpleasant | 4 (8%) | 11 (22%) |
| Pain on injection | 12 (24%) | 5 (10%) |
| Guess | | |
| Correct | 8 (16%) | 34 (67%)* |
| Incorrect | 21 (41%) | 2 (4%)* |
| No guess attempted | 22 (43%) | 15 (29%) |
| Induction | | |
| Pleasant | 35 (69%) | 24 (47%)* |
| Indifferent | 13 (25%) | 16 (31%) |
| Unpleasant | 0 | 7 (14%)* |
| No recall | 3 (6%) | 4 (8%) |
| Future preference | | |
| Same technique | 31 (61%) | 22 (43%) |
| No preference | 17 (33%) | 17 (33%) |
| Different technique | 3 (6%) | 12 (24%)* |

Based on the actual amount of i.v. drug used, the cost of induction of anaesthesia with propofol was £3.23 (0.60). On the basis of one ampoule of propofol per patient, this cost increased to £3.88. The cost of induction with 8% sevoflurane was £1.95 (0.56), which was significantly cheaper compared with propofol.

The average time from the start of induction of anaesthesia to completion of surgery was 10.0 (3.9) min in the propofol group and 10.2 (3.2) min in the sevoflurane group. There were no significant differences between groups in terms of the highest or lowest anaesthetic concentrations required during maintenance or in the delivered anaesthetic concentration at the end of anaesthesia (2.3 (0.9) % and 2.3 (0.8) % in the propofol and sevoflurane groups, respectively). Emergence times in the sevoflurane induction group (5.2 (2.2) min) were significantly faster compared with the propofol group (7.0 (3.2) min). There were no differences in subsequent recovery events between the two groups. Postoperative nausea (two) and vomiting (two) occurred in four patients in the sevoflurane group compared with none in the propofol group. This difference was not statistically significant.

## Discussion

This is the first double-blind comparison of induction of anaesthesia with sevoflurane and an i.v. agent. Our results suggest that sevoflurane is a practical induction agent for unpremedicated adult day-case patients. Although induction times with sevoflurane were slower compared with propofol, this difference was not of great clinical significance and was not obvious to the observer. Furthermore, the higher incidence of apnoea with propofol resulted in the end-point of anaesthesia accompanied by regular spontaneous ventilation being achieved significantly earlier with sevoflurane. Although this difference was also of limited clinical significance, the transition from induction to maintenance with sevoflurane was significantly smoother compared with propofol, with fewer patients coughing after induction. This difference is probably explained by the fact that when anaesthesia has been induced by inhalation, the inspired and alveolar anaesthetic concentrations are almost equilibrated, so that subsequent small changes in the depth of anaesthesia are readily achieved. In contrast, after induction of anaesthesia with an i.v. agent, the drug rapidly redistributes leading to a decrease in the depth of anaesthesia. During this period, it is necessary to introduce the maintenance agent rapidly in order to re-establish an adequate depth of anaesthesia. At the same time, stimulating events such as patient positioning, skin cleaning and surgical incision may be occurring, requiring a relatively greater depth of anaesthesia. The fact that our patients predominantly exhibited coughing during this period suggests that anaesthesia was sufficient to prevent purposeful movements, but inadequate to suppress reflex stimulation resulting from the presence of an oral airway or manipulation of the anatomical airway. It is possible that the transition from induction to maintenance would have been smoother had a concentration of sevoflurane greater than 2% been introduced in patients receiving propofol. However, the results of a pilot study suggested that this concentration was the best compromise to use in both groups of patients without unblinding the investigation.

Induction of anaesthesia with sevoflurane was associated with several other advantages. MAP was better maintained with sevoflurane compared with propofol and while the difference may be of limited significance for healthy patients, the relative hypotension associated with propofol may be disadvantageous in the elderly and coronary artery disease. Emergence from sevoflurane anaesthesia also occurred significantly faster when sevoflurane was used for induction compared with propofol. This difference was presumably because of the residual sedative effect of propofol and would probably not have been detectable after longer operations. However, this difference of only 2 min is probably of little, if any, clinical significance. Induction of anaesthesia with 8% sevoflurane was also significantly cheaper compared with propofol. In practice, the cost of i.v. induction depends on how much induction agent is actually drawn up and whether the remainder of the ampoule is discarded or used for the next patient. Although the manufacturers of propofol state that their ampoules are for single patient use, ampoule sharing occurs commonly. We therefore calculated the cost of propofol induction using the two extremes, that is on the basis of the exact amount of propofol required and on the basis of one ampoule per patient. Sevoflurane induction was substantially cheaper by both methods of comparison. Our calculation did not include the cost of the plastic syringe or of lignocaine required to reduce pain on injection of propofol. Sevoflurane costs did not include the (small) cost of nitrous oxide or the cost of obtaining and servicing the sevoflurane vaporizer. Costs common to both techniques (e.g. face mask and breathing system) were also not included.

Despite these advantages of sevoflurane over propofol, inhalation induction of anaesthesia was not as popular with our patients as the use of an i.v. induction agent. Although the majority of patients either had no preference or would choose the same anaesthetic again, a significant minority were unwilling to undergo further inhalation induction and several patients described this technique as "unpleasant". The most likely explanation for this finding was the odour reported by most patients receiving sevoflurane, and which 29% of these patients described as "unpleasant". In contrast, previous open (non-blinded) evaluations of sevoflurane have reported its odour to be pleasant[9 10] and have found inhalation induction popular with almost all patients.[5 9–12] Our patient population was chosen because cystoscopy is a short procedure without significant postoperative pain. It was therefore considered that these patients would have optimum postoperative recall of the induction period. More prolonged anaesthesia may have modified patients' recall of the induction process in these previous investigations. Although this comparison was double-blind, the possibility of patient bias cannot be excluded. This is suggested by the fact that more than 60% of patients receiving propofol also reported a smell during induction and patients were more inclined to guess that they had received an inhalation induction irrespective of the technique used. Patients undergoing cystoscopy have usually received multiple previous anaesthetics, often with the same anaesthetist, and are accustomed to a particular routine. Furthermore, these relatively elderly patients often have had personal experience of inhalation induction with older, less satisfactory anaesthetic agents. As a result, these patients are suspicious of any changes in anaesthetic practice, as indicated by a relatively high rate of refusal to consent to participate in this clinical study compared with our previous experience with other studies. Patients receiving propofol for induction of anaesthesia may have detected a residual smell from previous use of the anaesthetic system. In an attempt to reduce this possibility, the breathing system was flushed with oxygen between patients until the investigator could no longer smell sevoflurane.

Previous investigations have also used lower concentrations of sevoflurane for induction of anaesthesia. A tidal breathing technique in which 5% sevoflurane was inspired from the outset induced anaesthesia in 109–153 s and was tolerated well by adult patients pretreated with fentanyl.[4 5] Stepwise induction with 0.5% sevoflurane increased to a maximum of 4.5% also induced anaesthesia in a similar time, but was associated with excitatory activity in more than 30% of patients.[9] This level of excitement does not appear to be observed with more rapid induction of anaesthesia.[9] The use of 8% sevoflurane in a tidal breathing technique allowed more rapid induction of anaesthesia than reported in previous investigations with 5% sevoflurane and was also not associated with significant excitatory activity. The previous highest concentration of sevoflurane used for induction was 7.5%.[10] These authors reported coughing in 25% of patients receiving a tidal breathing induction technique with 7.5% sevoflurane, although coughing was reduced to 5% by a vital capacity breathing technique.[10] Interestingly, we observed coughing during induction in only one patient (2%) during tidal breathing with 8% sevoflurane. In the former study, the anaesthetic system was primed with 7.5% sevoflurane (in nitrous oxide) before being applied to the patients, whereas our patients initially breathed oxygen from a system to which sevoflurane and nitrous oxide were subsequently added. Because of mixing with oxygen within the breathing system, the concentration of sevoflurane at the mask would have reached a maximum more slowly and this may have minimized coughing. Nevertheless, the relatively high number of patients who described the smell of sevoflurane as unpleasant may have been as a consequence of using 8% sevoflurane rather than the lower doses used previously. Further work is needed to determine the optimum sevoflurane concentration and administration technique for induction of anaesthesia.

Four patients experienced postoperative nausea and vomiting (PONV) when anaesthesia was induced and maintained with sevoflurane compared with none when propofol was the induction agent. Our study was not designed with sufficient power to detect such a small difference in PONV as statistically significant. Nevertheless, propofol is known to have antiemetic effects which may persist into the postoperative period even when it is used solely as an induction agent.[13 14] It is possible therefore that this small difference in PONV is genuine, although with the small numbers involved it is unlikely to be of great clinical importance.

In summary, 8% sevoflurane was a practical induction agent for use in unpremedicated adult patients undergoing day-case cystoscopy. A slightly slower induction time with sevoflurane was offset by a reduced incidence of apnoea, earlier establishment of regular spontaneous ventilation, smoother transition to the maintenance phase, minimal depression of MAP during induction of anaesthesia, earlier emergence from anaesthesia and reduced induction costs. Although induction of anaesthesia with sevoflurane was acceptable to the majority of patients, a significant minority found it to be unpleasant and would prefer a different technique in the future. While it is possible that this finding was unique to the particular patient population chosen, inhalation induction may not prove as universally popular as i.v. induction. However, the technique may be particularly beneficial to patients with needle phobias or difficult venous access.

## Appendix

### CALCULATION OF INDUCTION COSTS

*Propofol*

Cost (£)=(List price of ampoule / 20)×induction dose (ml)

*Sevoflurane*

Cost (£)=Induction time (min)×fresh gas flow (ml)×set %× price of bottle / (100-set %)×bottle size (ml)×ml vapour per ml liquid anaesthetic (182.7)

*List prices used for this study*

| | |
|---|---|
| Propofol | £3.88 for a 20-ml ampoule |
| Sevoflurane | £49 00 for a 100-ml bottle. |

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# Rapid inhalation induction in children: 8% sevoflurane compared with 5% halothane

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## Summary

Sevoflurane has a lower blood-gas solubility and a less pungent odour than halothane; this may allow more rapid induction of anaesthesia. In a randomized, blinded study, we compared the induction characteristics of maximum initial inspired concentration of 8% sevoflurane and 5% halothane using conventional vaporizers in children aged 3 months to 3 years. There was no statistically significant difference in induction times between the two groups: mean times to loss of consciousness were 1 min 12 s (SD 18 s, range 40 s–1 min 44 s) for sevoflurane and 1 min 16 s (SD 17 s, range 50 s–1 min 52 s) for halothane, although these times were shorter than in previous studies using a gradual increase in vapour concentration. A small number of complications were noted in both groups, although none interfered with induction of anaesthesia. Struggling scores were lower in the sevoflurane group than in the halothane group (chi-square for trends=6.34, $P<0.02$). A significant number (11 of 15) of parents of children in the sevoflurane group who had previous experience of halothane induction preferred sevoflurane (chi-square for trends=4.03, $P<0.05$). We conclude that with this technique,induction was rapid with both sevoflurane and halothane. Our assessment of patient struggling and parents' perceptions suggests that induction with sevoflurane was more pleasant than with halothane. (*Br. J. Anaesth.* 1997; **78**: 362–365).

**Key words**
Anaesthetics volatile sevoflurane. Anaesthetics volatile, halothane. Anaesthetic techniques, induction. Children.

Sevoflurane is relatively non-irritant, and because of its low blood-gas solubility, it may have a rapid effect. It has recently been licensed for use in many countries around the world, and could therefore become the preferred inhalation induction agent for children.

Previous studies comparing the induction characteristics of sevoflurane and halothane in children used a technique in which the inspired concentrations were increased gradually, and only two of four showed that sevoflurane induced anaesthesia more rapidly than halothane.[1–4] It is possible however that a technique using high initial inspired concentrations of sevoflurane may be very rapid and we have therefore compared sevoflurane with halothane using maximum initial inspired concentrations delivered by conventional vaporizers in a randomized, blinded study.

## Patients and methods

We studied 52 patients, aged 3 months to 3 years, ASA I–III, allocated randomly to receive either sevoflurane or halothane for induction of anaesthesia. Patients were excluded if they had significant cardiac, respiratory, hepatic, renal, neurological or neuromuscular disease. There were two ASA III patients who had recurrent chest infections/ bronchiolitis from oesophageal stricture secondary to previous tracheo-oesophageal fistula and oesophageal reflux, respectively. The study was approved by the local Ethics Committee and parents gave informed written consent.

All patients received atropine 20 μg kg$^{-1}$ orally, 1 h before anaesthesia. No other premedication was prescribed and a parent was present at induction. Anaesthesia was induced by one of five anaesthetists using a standard technique. The anaesthetic was delivered by the use of a Mapleson F breathing system, with the anaesthetist holding the angle piece (without a mask) as close to the child's face as could be tolerated. The selected inhalation agent was administered with 66% nitrous oxide in oxygen at a vaporizer setting of either 5% for halothane or 8% for sevoflurane. The times taken to loss of consciousness (loss of eyelash reflex), acceptance of face mask and end of induction (small pupils, no gross bodily movements and regular respirations) were recorded for all patients by a trained observer. The

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vaporizers were concealed by a screen and adjusted by an anaesthetic assistant, with both the anaesthetist and the observer blinded to the selection of the anaesthetic vapour. During induction, the vaporizer setting could be reduced by stepwise reductions at the request of the anaesthetist if clinically indicated. When induction was complete, anaesthesia was continued with 2% halothane.

As soon as possible during induction of anaesthesia, which took place either on the parent's lap or on a trolley, pulse oximeter saturations (Ohmeda Biox 3740), heart rate (Simonsen & Weel Diascope DS 521) and non-invasive arterial pressure measurements (Dinamap 1640) were recorded at 1-min intervals. In some children it was possible to apply the pulse oximeter probe before induction, and in the remainder it was applied immediately after loss of consciousness. The first arterial pressure recording was obtained 1 min after loss of consciousness in the majority of cases. Any untoward events (cough, laryngospasm, secretions, breath-holding, vomiting, bronchospasm and excitement) were noted and scored (1 mild, 2=moderate, 3=severe). Movements before loss of consciousness were classified as struggling and those afterwards as excitement. A struggling score of 1 was given for head movement only, 2 for mild struggling with head and limb movements and 3 for more severe struggling. All observations and measurements were made and recorded by the same trained observer throughout the study. At the end of induction the anaesthetist was asked to give an opinion on which agent had been used.

Parents were interviewed the following day, either on the ward or by telephone if the child had already been discharged. They were asked specific questions where appropriate about how this induction compared with previous experience of inhalation induction of anaesthesia with halothane (How did this anaesthetic induction compare with previously? Better, identical or worse?).

Randomization was performed with random number tables. The Student's unpaired $t$ test was used for comparisons of induction times and lowest oxygen saturations. The chi-square test for trends was used to compare struggling scores and parental comparison with previous halothane anaesthesia. A test of the difference in proportions was used to compare the incidence of excitement with the two agents. Statistical significance was accepted when $P<0.05$.

## Results

Of the 52 patients studied, 27 received halothane and 25 received sevoflurane. One patient in the halothane group did not lose consciousness within 5 min, raising suspicion of equipment malfunction. The vaporizers were uncovered and the sevoflurane vaporizer was removed from the back bar. Induction then continued successfully with halothane. This patient was removed from the study, leaving complete data on 26 patients in the halothane group and 25 in the sevoflurane group. The distribution of age, weight and ASA grading was similar between the two groups (table 1). There were more boys because of inclusion of urological patients in the study.

*Table 1* Distributions of age, body weight, sex and ASA status in children anaesthetized with either sevoflurane or halothane (mean (SD or range) or number)

| | Halothane | Sevoflurane |
|---|---|---|
| *n* | 26 | 25 |
| Age (months) | 17.7 (3.1–30.4) | 16.0 (4.5–29.1) |
| Weight (kg) | 10.8 (3.1) | 10.6 (2.2) |
| Sex, (M/F) | 21/5 | 14/11 |
| ASA I/II/III | 16/9/1 | 12/12/1 |

Mean time to achieve loss of consciousness (loss of eyelash reflex) was shorter with sevoflurane (1 min 12 s; SD 18 s; range 40 s–1 min 44 s) than with halothane (1 min 16 s; 17 s; 50 s–1 min 52 s) but this small difference was not statistically significant ($P$=0.43) (fig. 1). Similarly, mean time to acceptance of the face mask (fig. 2) and mean time taken to complete induction (fig. 3) were slightly shorter in the sevoflurane group but the differences were not statistically significant between the two groups ($P$=0.47 and $P$=0.25, respectively). Loss of consciousness was achieved in less than 1 min in six patients in the sevoflurane group and in eight patients in the halothane group. In one patient in the

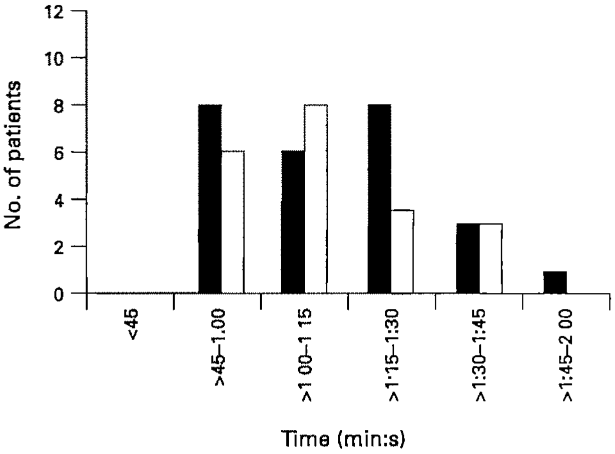

*Figure 1* Distribution of the time taken to loss of eyelash reflex in children who received induction of anaesthesia with either sevoflurane (☐) or halothane (■).

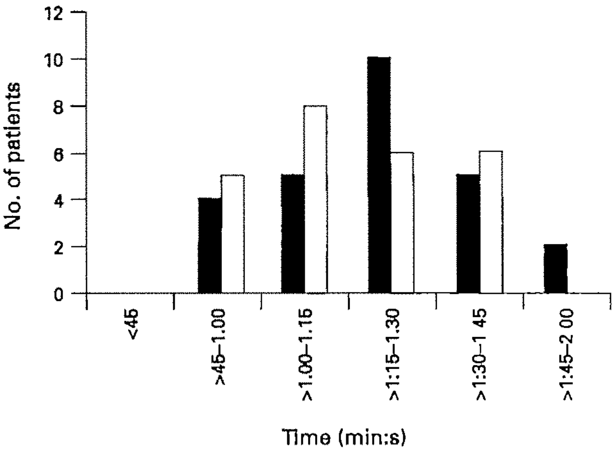

*Figure 2* Distribution of the time taken to acceptance of a face mask in children who received induction of anaesthesia with either sevoflurane (☐) or halothane (■).

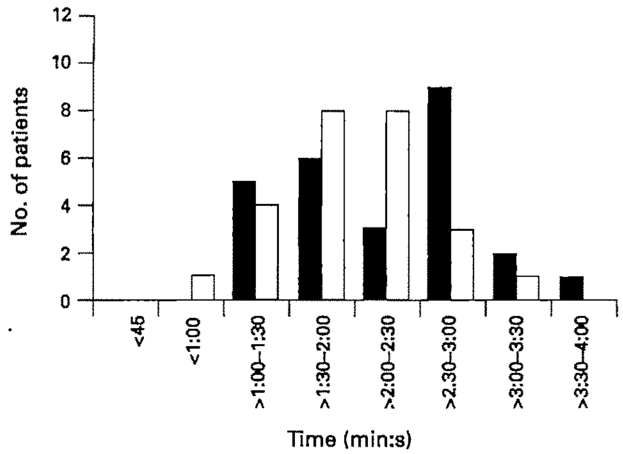

*Figure 3* Distribution of the time taken to complete induction of anaesthesia in children who received either sevoflurane (☐) or halothane (■).

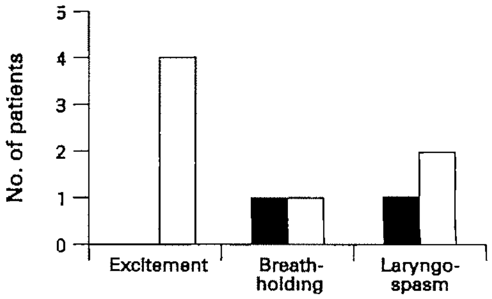

*Figure 5* Number of children who became excited, held their breath or had laryngospasm during induction of anaesthesia with either sevoflurane (☐) or halothane (■).

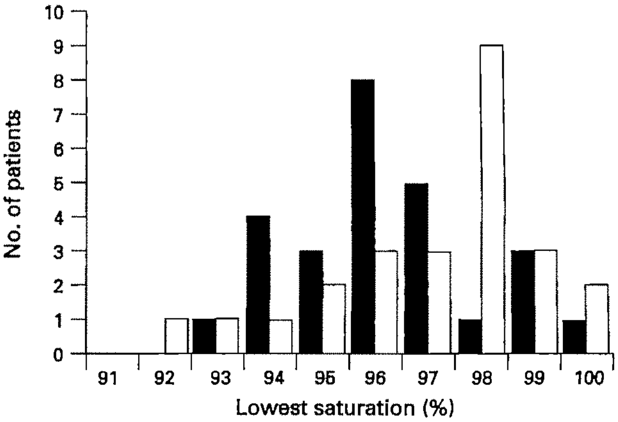

*Figure 6* Lowest pulse oximetry readings in children anaesthetized with either sevoflurane (☐) or halothane (■).

sevoflurane group, induction was completed within 1 min.

Seventeen children who received halothane were classified as having severe struggling compared with 10 in the sevoflurane group (fig. 4). Struggling scores were significantly lower in the sevoflurane group than in the halothane group (chi-square for trends=6.34, $P<0.02$).

Complications are summarized in figure 5; all were short lived and did not interfere with induction of anaesthesia. Excitement, defined as movements occurring after loss of consciousness, occurred in four patients in the sevoflurane group, two episodes of which were classified as severe. One patient who received sevoflurane demonstrated mild excitement, breath-holding and laryngospasm. The difference in the incidence of excitement was not statistically significant ($P=0.11$). No child vomited, had excess secretions, bronchospasm or coughed. Lowest and highest heart rates and arterial pressures were similar in both groups. Three patients had oxygen saturation values less than 94%, two in the sevoflurane group and one in the halothane group (fig. 6), but no patient had saturations less than 92%. Comparison of the lowest oxygen saturations showed no statistically significant differences between the two groups ($P=0.12$). There were no clinically significant episodes of desaturation in any patient. During induction of five patients, after loss of consciousness, the anaesthetist requested a reduction in the inspired vapour concentration to 50% of the initial setting. In one case this reduction was because of bradycardia (heart rate decreased from 162 to 71 beat $\text{min}^{-1}$) while receiving halothane and in the other cases (two in each group), this reduction was in response to clinically assessed hypoventilation.

Twenty-nine patients had undergone previous gaseous induction with halothane (15 in the sevoflurane group). The parents of 11 sevoflurane patients and three halothane patients preferred the study induction to previous experience (fig. 7). This difference was statistically significant (chi-square for trends=4.03, $P<0.05$).

The anaesthetists' opinions of which agent had been used were correct in 23 of 25 patients in the sevoflurane group, but in only 17 of 27 patients in the halothane group.

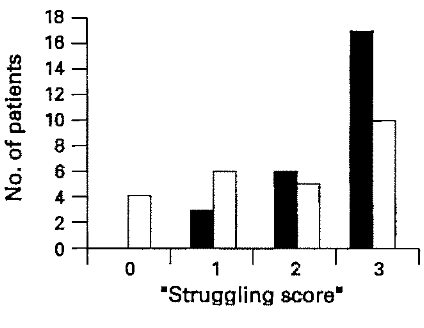

*Figure 4* Assessment of struggling of children who received induction of anaesthesia with either sevoflurane (☐) or halothane (■). 0=None, 1=head movement only, 2=head and limb movement, 3=severe struggling.

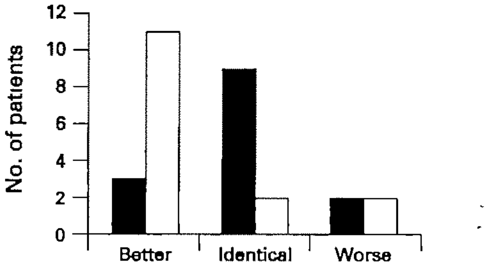

*Figure 7* Parents' comparison of the study induction using either sevoflurane (☐) or halothane (■) compared with previous halothane induction ($n=29$).

## Discussion

Inhalation induction remains a widely used technique in paediatric anaesthesia, particularly for small children in whom i.v. cannulation may be difficult. Because of its lack of airway irritation and smooth, relatively rapid induction qualities, halothane has remained the preferred agent for inhalation induction in children, despite its unpleasant odour, potential for hepatic damage[5] and increased incidence of arrhythmias. Sevoflurane has a lower blood-gas solubility and a less pungent odour, suggesting that induction may be more rapid than with halothane with a low incidence of complications during induction.

Our study demonstrated no significant difference between induction times for the two agents at maximum initial inspired concentrations. The sample size of 52 patients gave 80% power at the 5% level of detecting a difference in induction times of 14 s. However, the use of maximum inspired concentrations allowed us to achieve shorter induction times: 1 min 12 s and 1 min 16 s with sevoflurane and halothane, respectively, compared with 1 min 41 s and 2 min 17 s in a previous study undertaken at this institution using a gradual increase in vapour concentration.[1] These short induction times are in keeping with previous studies examining the use of high initial inspired concentrations of sevoflurane.[6 7]

The more rapid induction seen with sevoflurane compared with halothane in previous studies may reflect the fact that equivalent minimum alveolar concentrations were not used. We chose to compare inspired concentrations of 8% sevoflurane and 5% halothane, as these were the maximum concentrations that could be delivered by the vaporizers available to us. Based on published data, Lerman regards an inspired concentration of 7% sevoflurane as equivalent to 4.5% halothane, a similar ratio to that used in this study.[8] He does not believe that induction with sevoflurane should be faster than with halothane when over-pressure techniques are used, and the results of this study appear to support this view. To confirm this point, however, the anaesthetic would need to be delivered via a mask that was applied firmly to the face from the beginning of induction. This would probably be unacceptable in children when over-pressure is used, at least for induction with halothane.

Sevoflurane was not associated with any major airway complications, with a few episodes of mild breath-holding and laryngospasm. Although the use of atropine is not universal in this age group, unpublished data from our own laboratory suggest that the incidence of airway complications is higher in infants when it is not used. It is possible that the use of atropine as a premedicant in this study was a factor in minimizing the incidence of airway problems during induction. Excitement, a term used to describe involuntary movements occurring after loss of consciousness, occurred exclusively in the sevoflurane group, but did not interfere with the course of induction. This excitement occurred with a lower frequency than documented in previous studies[1 2] using a technique involving a gradual increase in sevoflurane concentration.

It is difficult to determine preference for any particular induction agent in patients of this age group, although adult volunteers have found the smell of sevoflurane more acceptable than halothane.[6] We have attempted to assess this factor, by assessing the degree of patient struggling during induction, and questioning the parents on the following day. Our results demonstrated that struggling was more severe in the halothane group. The majority of parents whose children received sevoflurane felt that the present anaesthetic was preferable to their previous halothane anaesthetic. We believe that these two results suggest a more pleasant induction for children with sevoflurane.

We did not detect any significant difference in the time taken to induce anaesthesia with sevoflurane compared with halothane when used with high initial inspired concentrations. Although the trained observer was at a sufficient distance from the patient so as not to be able to detect the odour, we suspected that blinding of the anaesthetists would be confounded by their ability to detect which agent was being administered. This was found not to be the case. Despite Lerman's prediction that induction times for the two agents would be similar when over-pressure was used, the speed of induction with halothane surprised us, and previously held assumptions may explain why the anaesthetists erroneously thought that 10 patients in the halothane group had been given sevoflurane.

The significant difference in struggling scores and in parental preference suggest that in children aged 3 months to 3 years, sevoflurane provided more pleasant induction.

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# Halothane–propofol anaesthesia for tracheal intubation in young children

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## Summary

In this double-blind, randomized study, we have investigated 100 healthy children, aged 3–6 yr. We compared intubating conditions and cardiovascular changes during light halothane anaesthesia and propofol 3 mg $kg^{-1}$ with those during deep halothane anaesthesia. Light halothane anaesthesia was defined as an end-tidal concentration of 1%, deep halothane anaesthesia as 2%. Intubating conditions were graded according to ease of laryngoscopy, vocal cord position and coughing. There were no statistically significant differences in the assessment of intubating conditions between the two groups; 94% of the children in the 1% halothane–propofol group and 100% of the children in the 2% halothane group had acceptable intubating conditions. Systolic arterial pressure decreased by 13% in the 1% halothane–propofol group compared with 20% in the 2% halothane group ($P<0.01$). (*Br. J. Anaesth.* 1997; **78**: 366–369).

**Key words**
Anaesthesia, paediatric. Anaesthetics i.v., propofol. Anaesthetics volatile, halothane. Intubation tracheal. Children.

The routine use of suxamethonium to facilitate tracheal intubation in children is controversial.[1] Severe side effects such as cardiac arrest and death have been reported in young children.[2] Even the use of non-depolarizing neuromuscular blocking agents may be associated with undesirable effects, such as prolonged neuromuscular block or the need to antagonize paralysis.[3] Therefore, tracheal intubation without the use of neuromuscular blocking agents is an alternative, especially for short procedures in paediatric anaesthesia. Deep halothane anaesthesia is suitable for tracheal intubation in children, but this inhalation agent is associated with cardiovascular depression.[4] Propofol has been studied for tracheal intubation in adults and children.[5–9] Adjuvant agents such as alfentanil and lignocaine improve intubating conditions.[5 9 10] A common side effect of propofol administration is pain on injection which can cause problems, especially in paediatric anaesthesia.[11–16] This can be avoided if propofol is administered after inhalation induction of anaesthesia by halothane. However, to date, no study has been undertaken on the intubating conditions and cardiovascular effects of propofol during halothane anaesthesia.

The aim of this study was to compare in children intubating conditions and cardiovascular side effects of light halothane anaesthesia in combination with propofol administration with deep halothane anaesthesia. Because propofol has not yet been licensed for children aged less than 3 yr, we limited this study to children aged 3–6 yr.

## Patients and methods

The Ethics Committee of the Hospital approved the study and written informed consent was obtained from parents.

In a prospective, randomized, double-blind design, we studied healthy children, aged 3–6 yr, ASA I or II. Children with a history of difficulties in tracheal intubation were excluded. All children were premedicated with midazolam 0.5 mg $kg^{-1}$ rectally, 30 min before induction of anaesthesia.

Fifty children being recruited into one of two groups: 2% halothane group=deep halothane anaesthesia, defined as an end-tidal halothane concentration of 2%; halothane–propofol group=light halothane anaesthesia, defined as an end-tidal halothane concentration of 1% combined with propofol 3 mg $kg^{-1}$. An independent nurse anaesthetist prepared syringes with propofol and placebo. Propofol was used as a 1% solution; 10% lipid emulsion was used as placebo.

On arrival in the anaesthetic room an electrocardiogram, pulse oximeter and non-invasive arterial pressure monitor (CMS-monitor, Hewlett-Packard) were attached. A side-stream connector for measurement of end-tidal halothane concentration and carbon dioxide was introduced between the face mask and anaesthetic tubing (side-stream gas analyser, Hewlett-Packard, M1025A).

Anaesthesia was induced with increasing concentrations of halothane and 67% nitrous oxide in oxygen, with a fresh gas flow of 6 litre $min^{-1}$, using a

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semi-closed circle system. When the child was asleep, an i.v. cannula was sited and the vaporizer was set to 3% in the 2% halothane group and to 1–1.5% in the halothane–propofol group. End-tidal halothane concentrations of 2% and 1%, respectively, were reached within 3–5 min. Spontaneous breathing was assisted and mild hyperventilation to an end-tidal carbon dioxide partial pressure ($P\text{E}'_{\text{CO}_2}$) of 4.2–4.4 kPa was established. Two anaesthetists were involved. Anaesthetist I performed the anaesthesia and anaesthetist II was in charge of the vaporizer and gas analyser. The vaporizer and gas analyser were not visible to anaesthetist I. Anaesthetist II gave commands to maintain a $P\text{E}'_{\text{CO}_2}$ of 4.2–4.4.kPa. He also set the vaporizer to maintain an end-tidal halothane concentration of 2% in the 2% halothane group and 1% in the halothane–propofol group. When the desired end-tidal halothane concentration was reached, 0.3 ml $\text{kg}^{-1}$ of the placebo (2% halothane group) or the propofol solution (halothane–propofol group) were administered over 15 s. Ninety seconds later tracheal intubation was performed. If tracheal intubation was not possible, suxamethonium 1.5 mg $\text{kg}^{-1}$ was given to facilitate intubation. After intubation, the lungs of all patients were ventilated with 1% halothane and 67% nitrous oxide in oxygen.

Heart rate (HR), arterial haemoglobin oxygen saturation ($Sp_{\text{O}_2}$) and arterial pressure (SAP) were noted before induction, after induction when end-tidal halothane concentration had reached 2% and 1%, respectively, 90 s after propofol or placebo administration, immediately after intubation, and 1 and 3 min after intubation. If HR was less than 80 beat $\text{min}^{-1}$, atropine 0.01 mg $\text{kg}^{-1}$ was given.

Intubating conditions were assessed by anaesthetist I on the basis of the scoring system devised by Helbo-Hansen, Ravlo and Trap-Andersen.[17] Ease of laryngoscopy, vocal cord position and coughing were estimated on four-point scales. Intubating conditions were judged acceptable when each individual category score was 2 or less.

The chi-square test was used for non-parametric data. Student's *t* test with Bonferrroni correction was used for parametric data. $P<0.05$ were regarded as statistically significant.

## Results

We studied 100 children, aged 3–6 yr. The two groups were comparable in age, weight and sex (table 1). Baseline values of SAP and HR did not differ significantly. All children in the 2% halothane group showed acceptable intubating conditions compared with 94% in the halothane–propofol group (table 2) (ns). For three children in the halothane–propofol group, coughing was judged to be moderate; in one of these children closing of the vocal cords was assessed and in another child the vocal cords were closed. In this child suxamethonium was given to facilitate tracheal intubation.

In both groups HR decreased significantly after induction of anaesthesia (fig. 1). Three children in the 2% halothane group and two children in the halothane–propofol group received atropine after induction because HR was less than 80 beat $\text{min}^{-1}$. After administration of atropine HR and SAP increased in these children. For this reason HR and SAP values of these five children are not given in figure 1 and table 3. After administration of propofol

*Table 1* Patient characteristics (mean (SD) or number)

| | 2% Halothane group ($n$=50) | 1% Halothane–propofol group ($n$=50) |
|---|---|---|
| Age (months) | 60 | 58 |
| Weight (kg) | 20 (6) | 18 (4) |
| Sex (M/F) | 24/26 | 23/27 |

*Table 2* Intubating conditions

| | Score | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Laryngoscopy | Easy | Fair | Difficult | Impossible |
| 2% Halothane | 49 | 1 | — | — |
| 1% Halothane-propofol | 49 | 1 | — | — |
| Vocal cords | Open | Moving | Closing | Closed |
| 2% Halothane | 49 | 1 | — | — |
| 1% Halothane–propofol | 46 | 2 | 1 | 1 |
| Coughing | None | Slight | Moderate | Severe |
| 2% Halothane | 50 | — | — | — |
| 1% Halothane–propofol | 47 | — | 3 | — |
| Intubating conditions | Acceptable | | Unacceptable | |
| 2% Halothane | 50 | | — | |
| 1% Halothane–propofol | 47 | | 3 | |

*Table 3* Percentage changes in SAP from baseline values (mean (SD))

| | 2% Halothane ($n$=47) | 1% Halothane–propofol ($n$=48) | $P$ |
|---|---|---|---|
| After induction | −20 (10)% | −13 (11)% | <0.01 |
| After placebo/propofol | −21 (9)% | −13 (11)% | <0.001 |
| After intubation | −16 (11)% | −8 (13)% | <0.01 |
| 1 min after intubation | −14 (12)% | −9 (12)% | ns |
| 3 min after intubation | −14 (10)% | −11 (11)% | ns |

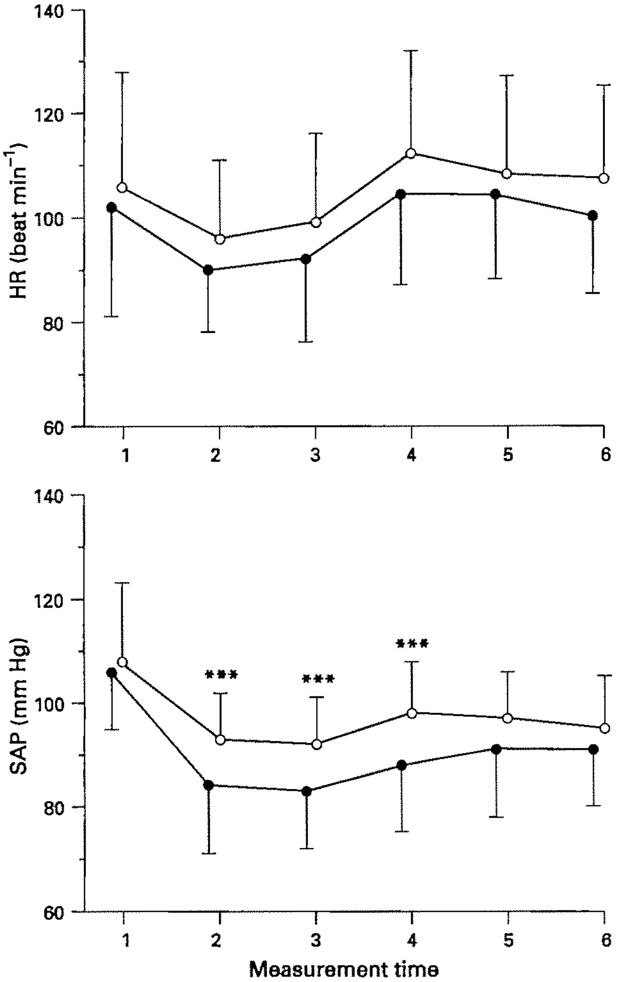

*Figure 1* Heart rate (HR) and systolic arterial pressure (SAP) responses in the 2% halothane (●) ($n$=47) and 1% halothane–propofol (○) ($n$=48) groups (mean (SD)). Measurement times: 1=before induction of anaesthesia; 2=after induction of anaesthesia; 3=after administration of propofol or placebo; 4=after tracheal intubation; 5=1 min after intubation; 6=3 min after intubation. ***$P$<0.001 between groups.

HR remained constant. After intubation HR increased in both groups. There were no significant differences in HR between the two groups. After induction of anaesthesia SAP decreased by 20% in the 2% halothane group compared with only 13% in the halothane–propofol group ($P$<0.01, table 3). After administration of propofol or placebo, SAP did not change significantly. After tracheal intubation SAP increased slightly, but SAP was still significant lower in the 2% halothane group.

## Discussion

Although suxamethonium produces good intubating conditions and has been used widely during the past 40 yr in paediatric anaesthesia, routine use in children is controversial because of its potential to induce masseter muscle spasm, malignant hyperthermia, hyperkalaemia and cardiac arrest.[1,2,18] Nondepolarizing neuromuscular blocking agents such as vecuronium or atracurium are poor alternatives because anaesthetic recovery may be delayed and neuromuscular block may be prolonged.[3]

Tracheal intubation without the use of neuromuscular blocking agents is an alternative. Deep halothane anaesthesia for tracheal intubation has been studied widely in children.[4,19,20] End-tidal halothane concentrations of 1.85% result in good intubating conditions in 95% of children aged 2–6 yr.[19] In a previous study, we assessed acceptable intubating conditions in 96% of children aged 1–5 yr at an end-tidal halothane concentration of 2%.[4] These findings were confirmed in the present study. Intubating conditions were evaluated as acceptable in all children in the 2% halothane group.

The most common side effect of deep halothane anaesthesia is cardiovascular depression. A decrease in arterial pressure of 18% has been reported by several authors[4,21,22] and this is similar to the changes observed in this study. The reduction in SAP during halothane anaesthesia is caused by a decrease in stroke volume and cardiac index.[21]

It is also possible to perform tracheal intubation without neuromuscular block by administration of propofol. McKeating, Bali and Dundee showed that conditions for laryngoscopy after propofol were superior to induction of anaesthesia with thiopentone in adults.[23] Addition of the short-acting opioid alfentanil further improved intubating conditions in adults[5–7] and children.[8,9] Intubating conditions were assessed as acceptable in 80% of children after alfentanil 15 μg kg$^{-1}$ and propofol 2.8–3.4 mg kg$^{-1}$.[9] The same incidence (80%) of acceptable intubating conditions was found by Steyn and co-workers in children aged 2–14 yr after alfentanil 15 μg kg$^{-1}$ and propofol 3–4 mg kg$^{-1}$ using the same intubating condition score as in this study.[8] We found a higher incidence (94%) of acceptable intubating conditions in children after administration of propofol 3 mg kg$^{-1}$ during 1% halothane anaesthesia. The combination of propofol and halothane seemed to decrease pharyngeal reflexes more reliably than propofol–opioid anaesthesia.

Induction of anaesthesia by inhalation of halothane avoids the problems of inserting a cannula into a vein in awake children and pain on injection of propofol, which is common, especially in children. The incidence has been reported as 6.6–50%.[12–16,24] Pretreatment with alfentanil or lignocaine reduces the incidence of pain only to 4–40%.[11]

The cardiovascular changes which were observed in the 1% halothane–propofol group were surprising. During 1% halothane anaesthesia SAP decreased by 13%. Administration of propofol 3 mg kg$^{-1}$ did not lead to a further decrease in arterial pressure. This is in contrast with other studies. Most authors reported a decrease in SAP by 15–28 % after propofol administration[12,14,16,25] caused by a decrease in stroke volume, cardiac index and systemic vascular resistance.[25] In all of these studies, anaesthesia was induced with propofol and maintained with halothane and nitrous oxide. The haemodynamic measurements were assessed when halothane had already been added to propofol. Therefore, these studies do not describe the haemodynamic changes of a single dose of propofol 2–3 mg kg$^{-1}$ in children. Murray and colleagues reported the haemodynamic effects caused by continuous infusion of propofol 0.4 mg kg$^{-1}$ min$^{-1}$ (with nitrous oxide) in children with a mean age of 4.8 yr. MAP decreased by 24% and stroke volume decreased by 22%.[26] As the dose of 0.4 mg $kg^{-1}$ $min^{-1}$ is very high, it is questionable if these results reflect the haemodynamic effects of a single dose of propofol. Further investigations are necessary to describe the cardiovascular effects of propofol used as a single dose or in combination with other anaesthetic agents in children.

We conclude that propofol administration during 1% halothane anaesthesia was a reliable method for tracheal intubation in children aged 3–6 yr. The incidence of acceptable intubating conditions was comparable with that during deep halothane anaesthesia, defined as an end-tidal halothane concentration of 2%, but cardiovascular depression was less during 1% halothane–propofol anaesthesia.

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*British Journal of Anaesthesia* 1997; **78**: 370–371

# Minimum alveolar concentration of desflurane for tracheal extubation in deeply anaesthetized, unpremedicated children

K. A. W. CRANFIELD AND L. M. BROMLEY

## Summary

We have studied 25 children, aged 4–9 yr, to determine the minimum alveolar concentration (MAC) of desflurane at which safe tracheal extubation can be performed in deeply anaesthetized children. The end-tidal concentration of desflurane was noted at tracheal extubation. Successful extubation was defined as one in which there was no coughing or bucking on the tracheal tube during suctioning of the pharynx, no movement or coughing within 1 min of tracheal extubation and no breath-holding or laryngospasm after extubation. Successful extubation was followed by extubation at a concentration of 0.5% less, and so on in subsequent subjects, until unsuccessful extubation occurred. After a reaction, the percentage was increased in the next patient, continuing up and down in pairs, until the required number of subjects was achieved. In 50% of children aged 4–9 yr, tracheal extubation may be accomplished without coughing or moving at an end-tidal concentration of 7.7%. The end-tidal concentration of desflurane to achieve satisfactory extubation in 95% of children was 8.5%. (*Br. J. Anaesth.* 1997; **78**: 370–371).

**Key words**
Anaesthetics volatile, desflurane. Intubation tracheal. Potency, anaesthetic, MAC. Anaesthesia, paediatric. Children.

Extubation of the trachea can be performed while the patient is deeply anaesthetized, or awake in a patient who has intact airway reflexes. The advantages of so called "deep extubation" are a reduction in coughing and other airway complications in situations where this is undesirable, for example during neurosurgery. Extubation during deep anaesthesia may also result in improved haemoglobin oxygen saturation compared with "awake extubation".[1]

The disadvantages of "deep extubation" are continuation of suppression of the laryngeal reflexes induced by general anaesthesia. This prevents coughing and may result in contamination of the airway. Partial or total airway obstruction may not be recognized.

These disadvantages should become less significant with an agent such as desflurane. Its low blood-gas solubility coefficient results in extremely rapid emergence and it would therefore be an ideal agent for "deep extubation".[2]

## Patients and methods

After obtaining Ethics Committee approval and informed consent from the parents or guardians, we studied 25 children, aged 4–9 yr (mean 6.0 yr). The children were ASA I or II, undergoing ear, nose and throat surgery: 10 patients were undergoing adenotonsillectomy, eight tonsillectomy and seven adenoidectomy with insertion of grommets.

The children were unpremedicated. Anaesthesia was induced using an inhalation technique with halothane and nitrous oxide in oxygen. An Ayre's T piece was used at fresh gas flows of 2.5 times the patient's minute volume. The trachea was intubated during deep halothane anaesthesia. When the airway was secure, halothane and nitrous oxide were discontinued and anaesthesia was maintained with desflurane in oxygen. The children were allowed to breathe spontaneously. Ventilation was assisted where necessary to maintain normocapnia.

End-tidal desflurane and carbon dioxide concentrations were measured using the Datex Capnomac Ultima monitor, sampling from the tracheal tube connector. The pharynx was suctioned before extubation and the patient's trachea extubated in the left lateral position while noting the end-tidal concentration of desflurane. There was no residual halothane or nitrous oxide at the time of extubation. A steady state concentration had been maintained for at least 10 min.

Unsatisfactory extubation was defined as one which resulted in coughing or bucking during suctioning of the pharynx, moving or coughing within 1 min of tracheal extubation, or produced laryngospasm or breath-holding. The investigator observing the response to extubation was independent from the anaesthetist responsible for controlling the end-tidal desflurane concentration. We chose a starting concentration of 12% because research on other volatile agents has shown that the optimal level for "deep extubation" is twice the MAC.[1]

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After successful extubation, the trachea of the next patient was extubated at 0.5% less than the previous patient. This continued in a stepwise fashion until unsuccessful extubation. The following patient's trachea was extubated at 0.5% more than the reactor, continuing up and down in a stepwise manner until the required number of patients was achieved.

When tracheal extubation was achieved, the children were given i.v. analgesia.

The number of patients and the methodology were modelled on a previous similar study to establish the safe dose of isoflurane for "deep extubation".[3]

### STATISTICAL ANALYSIS

Probit analysis was used to estimate the end-tidal concentration of desflurane at which extubation was achieved satisfactorily in 50% ($\text{MAC}_{\text{EX50}}$) and 95% ($\text{MAC}_{\text{EX95}}$) of patients. These were 7.7% (95% confidence limits 6.77–8.22%) and 8.5% (8.03–14.5%), respectively.

## Results

Figure 1 shows the response of each individual to tracheal extubation at varying end-tidal concentrations of desflurane.

Using the Mann–Whitney *U* test and the Wilcoxon rank sum *W* test, the ages, weights and steady state times did not influence the outcome of extubation.

Two patients developed laryngospasm at tracheal extubation; in both the trachea was extubated at end-tidal concentrations of 7.0% desflurane. One patient had undergone adenotonsillectomy and the other tonsillectomy alone. Laryngospasm resolved with application of positive pressure until the spasm settled. Oxygen saturation of both patients remained greater than 94%.

## Discussion

The $\text{MAC}_{\text{EX50}}$ in a deeply anaesthetized patient was established for isoflurane by Neelakanta and Miller.[3] This was defined as the alveolar concentration of inhalation anaesthetic at which 50% of patients undergoing tracheal extubation cough or move within 1 min of extubation or develop breath-holding or laryngospasm immediately after tracheal extubation.

"Deep extubation" is a useful technique in circumstances where coughing on the tracheal tube is undesirable. It has been suggested that "deep extubation" reduces episodes of desaturation in the emergence phase of anaesthesia.[1,4] Opponents of "deep extubation" argue that while the reflexes in the airway are obtunded, aspiration of foreign material can occur. Patients are also at risk of partial or total airway obstruction. Recovery staff need to be adequately trained and understand the possible complications involved in caring for the deeply unconscious patient.

Previous data suggested that despite its irritant nature, there is no increased incidence of coughing or airway irritation during emergence from desflurane anaesthesia.[2] The low blood-gas solubility coefficient of desflurane (0.42) and its low tissue–blood partition coefficient allow a more rapid decrease in the rate of elimination ($F\text{A}/F\text{A}_0$) compared with isoflurane and halothane. This makes it an ideal agent for "deep extubation" as it is eliminated rapidly, allowing prompt return of upper airway reflexes. Several studies have shown its rapid recovery characteristics in children and adults.[5,6]

In conclusion, the safe MAC value of desflurane for successful deep extubation in 50% of anaesthetized school-aged children was 7.7%. This is approximately the same value quoted for the MAC of this agent in children of 5–12 yr (established as mean 7.98 (SD 0.43)%). We have demonstrated that the safe concentration in oxygen was approximately 8.5% and therefore we would expect that safe "deep extubation" should be possible at a concentration of at least 8.0% in the presence of nitrous oxide and analgesics.

## Acknowledgements

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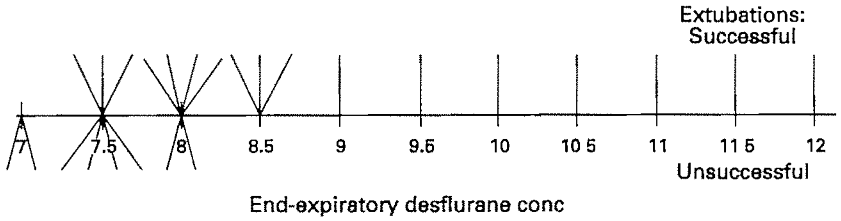

*Figure 1* Data for each patient's response to tracheal extubation Each individual is represented by a line.

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# Increase in serum creatine phosphokinase concentrations after suxamethonium during sevoflurane or isoflurane anaesthesia in children

A. Kudoh, T. Sakai, H. Ishihara and A. Matsuki

## Summary

We have studied whether sevoflurane or isoflurane anaesthesia modulates the effect of suxamethonium on serum concentrations of enzyme markers of skeletal muscle function in paediatric patients. Eighty patients undergoing bilateral tonsillectomy, aged 5–12 yr, were allocated randomly to receive anaesthesia with either sevoflurane and nitrous oxide or isoflurane and nitrous oxide. Serum creatine phosphokinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) concentrations were measured before, and at 30 min and 20 h after induction of anaesthesia. Mean CK concentrations increased from 97.0 (SD 17.3) to 478 (170) iu litre$^{-1}$ in the sevoflurane group and from 86.9 (22.4) to 628 (223) iu litre$^{-1}$ in the isoflurane group, 20 h after induction of anaesthesia. Mean peak serum CK concentration in the sevoflurane group (478 (170) iu litre$^{-1}$) was significantly less ($P<0.05$) than that in the isoflurane group (628 (223) iu litre$^{-1}$). Mean serum AST concentration increased from 17.5 (4.9) to 31.7 (3.5) iu litre$^{-1}$ in the sevoflurane group and from 17.3 (2.4) to 34.8 (5.7) iu litre$^{-1}$ in the isoflurane group, 20 h after induction of anaesthesia. Mean peak serum AST concentrations in the sevoflurane group were significantly lower ($P<0.05$) than those in the isoflurane group. There were no significant differences in serum ALT or LDH concentrations between the groups either before or after anaesthesia. We conclude that administration of suxamethonium during either sevoflurane or isoflurane anaesthesia caused a marked increase in serum CK concentrations in paediatric patients. The clinical significance of this finding is uncertain. (*Br. J. Anaesth.* 1997; **78**: 372–374).

**Key words**
Anaesthesia, paediatric. Anaesthetics volatile, sevoflurane. Anaesthetics volatile, isoflurane. Enzymes, creatine phosphokinase. Neuromuscular block, suxamethonium. Children.

Sevoflurane has a low blood-gas partition coefficient (0.63) and the lowest pungency[1–3] of commercially available inhalation anaesthetics. Thus a rapid increase in alveolar and tissue anaesthetic partial pressure is achieved easily during induction with sevoflurane, and in children its haemodynamic effects are less than that of halothane.[4] Because of these characteristics, this agent is the most frequently used for induction of anaesthesia in paediatric patients.

Serum creatine phosphokinase (CK) concentrations increase more in children than in adults after i.v. administration of suxamethonium during either halothane or enflurane anaesthesia.[5 6] Peak serum CK concentrations are reported to occur at 9–24 h after administration of suxamethonium. However, data on serum CK concentrations for this period during sevoflurane and isoflurane anaesthesia have not been reported. Thus this study was designed to determine serum concentrations of CK and other enzymes before and after suxamethonium during sevoflurane or isoflurane anaesthesia in paediatric patients.

## Patients and methods

The study was approved by the Institutional Ethics Committee and informed consent was obtained from a parent of each patient. We studied 80 ASA I paediatric patients, aged 5–12 yr, undergoing bilateral tonsillectomy.

Patients were allocated randomly to one of two groups to receive either sevoflurane or isoflurane. All patients were premedicated with oral diazepam 0.3 mg kg$^{-1}$, 60 min before induction of anaesthesia. Anaesthesia was induced in 40 patients with 5.0% sevoflurane in combination with nitrous oxide 2 litre min$^{-1}$ and oxygen 2 litre min$^{-1}$. Anaesthesia was maintained with 2.5% sevoflurane and 50% nitrous oxide in oxygen. The remaining 40 patients received 3.0% isoflurane and nitrous oxide 2 litre min$^{-1}$ and oxygen 2 litre min$^{-1}$ during induction. Anaesthesia was maintained with 1.5% isoflurane and 50% nitrous oxide in oxygen. I.v. suxamethonium 1 mg kg$^{-1}$ was given to facilitate tracheal intubation in

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both groups. End- expiratory concentrations of oxygen, carbon dioxide and anaesthetics were monitored using a 5250 RGM analyser (Ohmeda, Madison, WI, USA). Lactated Ringer's solution was infused at a rate of 4 ml kg$^{-1}$ h$^{-1}$ to all patients. The lungs were ventilated mechanically to maintain $PE'_{CO_2}$ at 4.8–5.6 kPa. Rectal temperature was monitored continuously with an electric thermistor and maintained at 36.5–37.5 °C using a warming blanket. Postoperative pain relief was provided by rectal diclofenac sodium 12.5–25 mg every 6 h as needed.

Fasciculations after administration of suxamethonium and postoperative muscle pain the day after surgery were evaluated in all patients. Blood samples were obtained just before, and 30 min and 20 h after induction of anaesthesia. CK was measured using a modification of the Rosalki's method with a Paramax kit from Baxter (Deerfield, USA).[7] Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations were measured using a modification of the method of the Scandinavian Society of Clinical Chemistry with a Paramax kit from Baxter (Deerfield, USA).[8] Lactate dehydrogenase (LDH) concentration was measured according to a modification of the method of Gay and colleagues using a Paramax kit.[8] The CK method has a sensitivity of 0.091 mAd min$^{-1}$ iu$^{-1}$ litre$^{-1}$ and a coefficient of variation (cv) of less than 2%. The AST, ALT and LDH assays have a sensitivity of 0.182 mAd min$^{-1}$ iu$^{-1}$ litre$^{-1}$ and a cv of less than 7%. Normal ranges are 38–173 iu litre$^{-1}$ for CK, 12–45 iu litre$^{-1}$ for AST, 7–40 iu litre$^{-1}$ for ALT and 180–387 iu litre$^{-1}$ for LDH.

Data, expressed as mean (SD), were analysed using the Student's $t$ test for paired and unpaired samples. $P<0.05$ was considered statistically significant.

## Results

There were no significant differences between the two groups in age, weight, duration of surgery and anaesthesia, or rectal temperature (table 1). Laryngospasm, bronchospasm and masseter muscle spasm did not occur in any patient during induction of anaesthesia. Systolic and diastolic arterial pressures and heart rate during anaesthesia were similar in both groups.

Postoperative muscle pain was reported by 33% of patients in the sevoflurane group and by 43% in the isoflurane group. There were no significant differences in serum concentrations of CK or AST between patients with and without muscle pain. Fasciculations were observed in 18% of patients in the sevoflurane and in 15% of patients in the isoflurane group. There were no significant differences in serum concentrations of CK or AST between patients with and without fasciculations. In addition, we did not observe any significant correlation between age and CK concentrations during sevoflurane or isoflurane anaesthesia.

*Table 1* Patient characteristics in the sevoflurane and isoflurane groups (mean (SD or range) or number)

| | Sevoflurane ($n$=40) | Isoflurane ($n$=40) |
|---|---|---|
| Age (yr) | 7.5 (5–11) | 8.0 (5–12) |
| Weight (kg) | 26.9 (9.9) | 27.7 (12.1) |
| Sex (M/F) | 18/22 | 17/23 |
| Anaesthesia time (min) | 60.6 (17.4) | 67.3 (13.5) |
| Operative time (min) | 48.3 (12.7) | 51.7 (14.8) |
| Maximum rectal temperature during anaesthesia (°C) | 37.3 (0.5) | 37.0 (0.6) |
| Maximum rectal temperature after anaesthesia (°C) | 37.4 (0.7) | 37.1 (0.9) |

*Table 1* Serum CK, AST, ALT and LDH concentrations before and after the administration of suxamethonium (mean (SD)). *$P<0.05$ compared with isoflurane; †$P<0.05$ compared with pre-anaesthetic value

| | Sevoflurane ($n$=40) | Isoflurane ($n$=40) |
|---|---|---|
| CK (iu litre$^{-1}$) | | |
| Before anaesth. | 97.0 (17.3) | 86.9 (22.4) |
| 20 h after anaesth. | 478 (170)*† | 628 (223)*† |
| AST (iu litre$^{-1}$) | | |
| Before anaesth. | 17.5 (4.9) | 17.3 (2 4) |
| 20 h after anaesth. | 31.7 (3.5)*† | 34.8 (5 7)*† |
| ALP (iu litre$^{-1}$) | | |
| Before anaesth. | 7.7 (3.1) | 8.0 (2 9) |
| 20 h after anaesth. | 8 8 (2.8) | 11.2 (3 0) |
| LDH (iu litre$^{-1}$) | | |
| Before anaesth. | 326 (60.9) | 335 (55.3) |
| 20 h after anaesth. | 395 (72.8) | 390 (68.4) |

Mean basal serum CK concentrations in the sevoflurane group were 97.3 (SD 17.3) iu litre$^{-1}$ before anaesthesia, which increased to 478 (170) iu litre$^{-1}$ ($P<0.05$) 20 h after injection of suxamethonium. In the isoflurane group, basal serum CK concentrations were 86.9 (22.4) iu litre$^{-1}$ before anaesthesia and 628 (223) iu litre$^{-1}$ ($P<0.05$) 20 h after injection of suxamethonium. Basal AST concentrations in the sevoflurane group were 17.5 (4.9) iu litre$^{-1}$ before anaesthesia, which increased significantly to 31.7 (3.5) iu litre$^{-1}$ ($P<0.05$) 20 h after suxamethonium. In the isoflurane group, basal serum AST concentrations were 17.3 (2.4) iu litre$^{-1}$ before anaesthesia, increasing significantly to 34.8 (5.7) iu litre$^{-1}$ ($P<0.05$) 20 h after administration of suxamethonium. Mean serum CK and AST concentrations in the sevoflurane group were significantly lower ($P<0.05$) than those in the isoflurane group, 20 h after suxamethonium. Mean serum CK and AST concentrations 30 min after administration of suxamethonium were 113.4 (6.5) and 20.3 (1.7) iu litre$^{-1}$ in the sevoflurane group and 115.8 (7.0) and 22.1 (2.3) iu litre$^{-1}$ in the isoflurane group. There were no significant differences in serum ALT and LDH concentrations between groups, 30 min and 20 h after suxamethonium (table 2).

## Discussion

Suxamethonium is known to increase serum CK and myoglobin concentrations when given during halothane or enflurane anaesthesia and to produce larger increases in serum concentrations of these enzymes in paediatric patients.[5 6] It has been reported that plasma CK and myoglobin concentrations do not correlate with fasciculations after suxamethonium,[9] although children are known not to fasciculate. Increased CK concentrations in children after suxamethonium could be caused by muscle prematurity, making the muscle prone to release CK or to increase muscle content of CK.[5]

Tano and Fujiwara[10] reported that serum CK concentrations 20 min after administration of suxamethonium during sevoflurane anaesthesia were similar to those during halothane anaesthesia. Noguchi and colleagues[11] found that serum CK and myoglobin concentrations after suxamethonium were lower in patients receiving sevoflurane than in those receiving halothane 60 min after suxamethonium. However, in these studies CK concentrations were measured 20 and 60 min after suxamethonium, well before serum CK concentration reaches its peak, at 9–24 h after administration of suxamethonium.[6]

In our study, serum CK concentrations, measured 20 h after suxamethonium, were increased markedly in both groups, in contrast with findings of previous reports.[5 11 12] Moreover, we found that the peak serum concentration of CK was higher in the isoflurane than in the sevoflurane group. The increased serum CK originated from skeletal muscle where most of the enzyme is located. Acute muscle necrosis or sudden changes in the permeability of the sarcolemma may be responsible for the increase in serum CK concentrations.[13] Serum increases in AST concentrations were also caused by damage to skeletal muscle because postoperative ALT and LDH values were unchanged. Thus differences in serum CK and AST concentrations between both groups may be related to differences in the effects of both anaesthetics on skeletal muscle. The reasons for the higher CK concentrations during isoflurane anaesthesia are unclear. We hypothesize that the immaturity of skeletal muscle in children makes it either prone to release more CK or be richer in CK. In addition, differences in concentrations of CK and AST after suxamethonium between the two anaesthetics may result from differences in intracellular reactions triggered by anaesthetics or from differences in the permeability of the muscle cell membrane to anaesthetics. Using skinned fibres, isoflurane was more potent than sevoflurane, producing $Ca(^{2+})$-induced $Ca^{2+}$ release (CICR).[14] CICR, which plays an important role in the diagnosis of malignant hyperthermia (MH), may not be directly related to CK release. However, it is interesting that isoflurane, which was more potent than sevoflurane in the test for MH, was also associated with higher concentrations of CK after suxamethonium in our study.

Heart muscle, liver, skeletal muscle and kidney are rich in AST and ALT. LDH is present in high concentration in the kidney, heart muscle and skeletal muscle. AST, ALT and LDH increase in the presence of severe muscle damage. In this study, both CK and AST increased significantly while ALT and LDH did not. The increase in CK during surgery is caused mainly by skeletal muscle injury. However, in our study it was probably a result of an increase in muscle membrane permeability, because minor surgery such as tonsillectomy has little effect on skeletal muscle. Thus the mechanism leading to increased CK in our study is probably different from that after exercise. In our study, serum CK concentrations were increased markedly by suxamethonium 1 mg $kg^{-1}$ in combination with both anaesthetics. A higher amount of suxamethonium would probably lead to higher serum CK concentrations.

In summary, we have demonstrated that sevoflurane preserved skeletal muscle integrity more than isoflurane when suxamethonium was used during induction of anaesthesia. However, because of the marked increase in serum CK concentrations with both anaesthetics, anaesthetists should carefully weigh the risks and benefits of the use of suxamethonium in children during isoflurane or sevoflurane anaesthesia, in spite of the fact that no clinical signs were observed in this study.

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*British Journal of Anaesthesia* 1997; 78: 375–377

# Hypnotic effect of i.v. propofol is enhanced by i.m. administration of either lignocaine or bupivacaine

I. BEN-SHLOMO, M. TVERSKOY, G. FLEYSHMAN AND G. CHERNIAVSKY

## Summary

We have compared the hypnotic requirements for i.v. propofol when combined with i.m. lignocaine or bupivacaine. Ninety women (ASA I, II) undergoing minor gynaecological surgery were allocated randomly to one of nine groups of 10 patients to receive propofol combined with i.m. lignocaine, bupivacaine or saline, respectively. Propofol was administered in bolus doses of 0.2 mg kg$^{-1}$ every 30 s until loss of response to verbal command was achieved. Lignocaine and bupivacaine significantly enhanced the hypnotic effect of propofol in a dose-dependent manner. The maximum doses tested (lignocaine 3.0 mg kg$^{-1}$ and bupivacaine 1.0 mg kg$^{-1}$) reduced the hypnotic dose of propofol by 34.4% and 39.6%, respectively. We conclude that if lignocaine or bupivacaine is injected into soft tissue before induction of anaesthesia by propofol, the i.v. dose of the latter should be modified accordingly. (*Br. J. Anaesth.* 1997; **78**: 375–377).

**Key words**
Anaesthetics i.v., propofol. Anaesthetics local, lignocaine. Anaesthetics local, bupivacaine. Interactions (drug).

There is a growing interest in possible interactions of local and regional anaesthesia with drugs used for general anaesthesia.[1–5] Recently, we have shown that bupivacaine-induced spinal block significantly reduced the hypnotic requirements for thiopentone, midazolam and propofol.[3 4] Interestingly, the magnitude of this effect was not uniform for all of these drugs, which suggests an effect additional to, and distinct from, spinal block. However, no systematic evaluation of the effect of lignocaine on the hypnotic requirements of propofol was carried out.

A possible drug interaction with local anaesthetics which may modify the effect of general anaesthetics is of clinical relevance. At times, a dose of local anaesthetic is injected to provide pain relief for a surgical procedure, but is either insufficient or ineffective. When this happens, the anaesthetist is faced with a patient who already received a dose of local anaesthetic drug into a soft tissue location, but still needs general anaesthesia.

In order to evaluate possible interactions between lignocaine and bupivacaine, we have carried out this prospective, double-blind study.

## Patients and methods

With informed consent and approval of the Institutional Review Board, we studied 90 women, aged 20–50 yr, ASA I or II, weighing 50–90 kg, undergoing minor elective gynaecological surgery. Patients did not receive premedication and were allocated randomly to one of nine subgroups, divided further into three groups: in group 1, 40 patients received one of four doses of i.m. 4% lignocaine (0.5, 1.0, 2.0 and 3.0 mg kg$^{-1}$, 10 patients for each dose), administered into the gluteus muscle 10 min before induction of anaesthesia; in group 2, 40 patients received one of four doses of i.m. 0.5% bupivacaine (0.25, 0.5, 0.75 and 1.0 mg kg$^{-1}$, 10 patients for each dose), administered into the gluteus muscle 30 min before induction of anaesthesia. Intervals between i.m. injection of lignocaine or bupivacaine and i.v. injection of propofol were planned in the light of pharmacokinetic considerations regarding injection of these local anaesthetics into skeletal muscle or fat tissue.[6] Administration of the hypnotic drug was scheduled therefore to achieve these intervals. In group 3, 10 patients served as controls who received i.m. saline 3 ml into the gluteus muscle 10 min before induction of anaesthesia. No patient complained of local pain at the injection site that lasted for more than a few seconds.

Inability to respond to a simple command was used as the end-point for hypnosis ("open your eyes!", said twice). Propofol was administered i.v. over 5 s in bolus doses of 0.2 mg kg$^{-1}$ every 30 s. Response to verbal commands was evaluated 25 s after each bolus. The total dose required to achieve loss of response in each patient was recorded in mg kg$^{-1}$.

One physician administered propofol and monitored the response to verbal command (G. C.). He was unaware of the dose or type of local anaesthetic (or saline) administered earlier. On completion of the experimental evaluation, anaesthesia was continued and complemented with additional agents, as indicated clinically.

Analysis of variance (ANOVA) was used to evaluate the difference between the subgroups of 10

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patients, as reflected by *t* test. A simple regression analysis was used to evaluate the significance of trends. $P<0.05$ was regarded as the threshold for significance.

## Results

There were no differences in age or weight between the nine subgroups of 10 patients (table 1). The mean dose of propofol for hypnosis in group 3 (control) was 1.844 (SD 0.273) mg kg$^{-1}$. Progressive reduction of the hypnotic dose was noted for both lignocaine and bupivacaine (figs 1, 2, respectively). The lowest doses of lignocaine and bupivacaine tested (0.5 and 0.25 mg kg$^{-1}$, respectively) did not reduce significantly the hypnotic dose of propofol. The first dose of lignocaine which significantly reduced the hypnotic dose of propofol was 1.0 mg kg$^{-1}$, and that for bupivacaine 0.5 mg kg$^{-1}$. The highest doses of lignocaine and bupivacaine tested in this study (3.0 mg kg$^{-1}$ and 1.0 mg kg$^{-1}$, respectively) reduced the hypnotic requirements for propofol by 34.4% and 39.6%, respectively. The trends in reduction (on a log-dose scale) in propofol hypnotic requirements were $r^2$=0.476 and $r^2$=0.706 for lignocaine and bupivacaine, respectively ($P$=0.0001 in both cases). The respective slopes of the two curves were −0.612 (95% confidence interval −0.437 to −0.823) and −1.064 (−1.29 to −0.876), indicating a significantly steeper curve for bupivacaine.

*Table 1* Age (mean) and weight (mean (SD)) in the different groups of patients in the study on the interaction between propofol and local anaesthetics

| Group | Local anaesthetic (mg kg$^{-1}$) | | Age (y) | Weight (kg) |
|---|---|---|---|---|
| 1 | Lignocaine | 0.5 | 30.7 | 64.2 (8.3) |
| | | 1.0 | 38.8 | 59.4 (10.3) |
| | | 2.0 | 38.0 | 68.8 (12.4) |
| | | 3.0 | 35.1 | 66.5 (10.4) |
| 2 | Bupivacaine | 0.25 | 34.2 | 68.5 (8.7) |
| | | 0.50 | 33.5 | 63.6 (8.4) |
| | | 0.75 | 33.9 | 62.9 (6.8) |
| | | 1.00 | 34.9 | 65.6 (6.7) |
| 3 | Saline 3 ml | | 32.8 | 63.1 (9.2) |

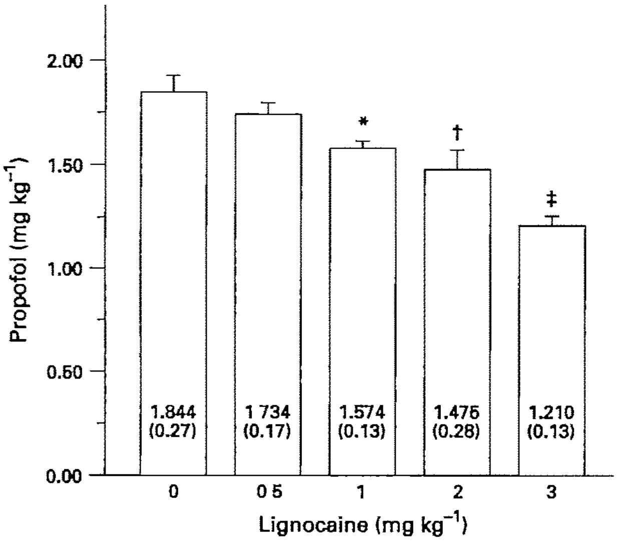

*Figure 1* Enhancement of the i.v. propofol hypnotic effect by i.m lignocaine. Each bar represents the mean (SEM) dose required to achieve loss of response to verbal commands in a group of 10 women. The values inside each bar are the actual doses (SD) in mg kg$^{-1}$. *$P<0.05$ compared with control; †$P<0.05$ compared with control and lignocaine 0.5 mg kg$^{-1}$; ‡$P<0.05$ compared with control and lignocaine 0.5 and 1.0 mg kg$^{-1}$.

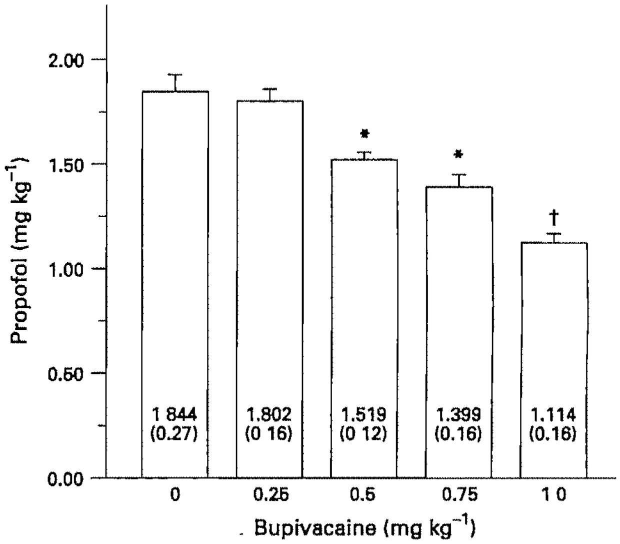

*Figure 2* Enhancement of the i.v. propofol hypnotic effect by i.m. bupivacaine. Each bar represents the mean (SEM) dose required to achieve loss of response to verbal commands in a group of 10 women. The values inside each bar are the actual doses (SD) in mg kg$^{-1}$. *$P<0.05$ compared with control or bupivacaine 0.25 mg kg$^{-1}$; †$P<0.05$ compared with control and all lower doses of bupivacaine.

## Discussion

The hypnotic dose of propofol for the control group in this study (mean 1.844 (SD 0.273) mg kg$^{-1}$) was within the recommended range for induction of anaesthesia (1.5–3.0 mg kg$^{-1}$).[7] The highest doses of local anaesthetics were less than half the recommended maximum clinical doses.[6] Local anaesthetics are known to have some influence on the central nervous system[8] which are not unlike some of the characteristics of general anaesthetics. The interaction between local anaesthetics and propofol was tested mainly for two aspects of their common use; namely, alleviation of local pain caused by propofol[9] and use of local lignocaine preparations to blunt cardiovascular responses to tracheal intubation.[10] It has been reported that mucosal absorption is less than that observed with direct injection.[11] Nevertheless, in the above studies possible modification of the hypnotic dose of propofol was not the central issue. In our study the interval between i.m. lignocaine or bupivacaine and i.v. administration of propofol was planned to be 10 and 30 min, respectively, because at these intervals blood concentrations of these agents reach a peak.[6] These intervals to peak blood concentrations are very close to those seen after extradural administration of both drugs.[12 13] Thus systemic interaction, superimposed on decreased afferent input, is most likely to be of the same nature.

The clinical relevance of our results lies in the growing use of local and regional alternatives for general anaesthesia, alternatives that do not invariably provide adequate pain relief. This in turn may lead to induction of general anaesthesia after previously injected local anaesthetics; in this situation physicians should be alert to the nature of the above interaction. Moreover, special attention should be devoted to bupivacaine as its interaction with propofol seemed to form a steeper curve. Whether the two local anaesthetics tested herein interact in the same way and magnitude with other general anaesthetics is currently under study.

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# Occupational exposure to desflurane and isoflurane during cardiopulmonary bypass: is the gas outlet of the membrane oxygenator an operating theatre pollution hazard?

K. HOERAUF, M. HARTH, K. WILD AND J. HOBBHAHN

**Summary**

We have compared occupational exposure to isoflurane and desflurane during cardiopulmonary bypass, with and without a scavenging system at the membrane oxygenator outlet. Trace concentrations of volatile anaesthetics were measured by a direct reading instrument in 40 elective heart surgery procedures. Measurements were obtained in the breathing zones of the anaesthetist and perfusionist. When a scavenging system was used, median desflurane values were less than 0.3 ppm and isoflurane values less than 0.2 ppm. Without a scavenging system values were, in general, three- (isoflurane) to five- (desflurane) fold higher. We conclude that the use of a scavenging system at the membrane oxygenator outlet can reduce occupational exposure to volatile anaesthetics. We therefore recommend routine use of scavenging devices during cardiopulmonary bypass. (*Br. J. Anaesth.* 1997; 78: 378–380).

**Key words**
Anaesthetists, occupational exposure. Heart, cardiopulmonary bypass. Anaesthetics volatile, isoflurane. Anaesthetics volatile, desflurane. Operating rooms, contamination. Equipment, scavenging devices.

Exposure to traces of inhaled anaesthetic agents may impair the health of the operating theatre (OT) personnel. Although no cause–effect relationship has been found, most public health authorities recommend various occupational exposure standards to minimize possible health risks.[1] In the UK, a 50 ppm isoflurane occupational exposure standard as an 8-h time-weighted average has been published recently.[2] Occupational exposure standards for sevoflurane and desflurane have not yet been established.

Several efforts have been made to minimize exposure by improving the working environment. Effective air conditioning and scavenging of the anaesthesia machine outlets are used routinely to maintain waste gas concentrations low. Nevertheless, gas outlet ports on membrane oxygenators are not routinely connected to operating theatre exhaust systems, even though anaesthetic gases are being released at high flow rates (>5 litre $\text{min}^{-1}$) into the operating theatre.

The aim of this study was to determine exposure of the anaesthetist and perfusionist to desflurane and isoflurane during cardiopulmonary bypass, with and without the use of a scavenging system at the oxygenator outlet.

## Patients and methods

After approval by our institutional review board, we studied 40 patients (28 males), median age 64 (range 36–82) yr, undergoing elective coronary artery surgery. Patients were premedicated with clorazepate 20–30 mg orally on the evening before surgery, and clorazepate 20 mg approximately 1 h before operation. Anaesthesia was induced with fentanyl 5 $\mu g\ kg^{-1}$ i.v., followed by a sleep dose of etomidate. Neuromuscular block was produced with pancuronium 100 $\mu g\ kg^{-1}$. Anaesthesia was maintained before CPB with an infusion of propofol 5 mg $kg^{-1}\ h^{-1}$, supplemented with fentanyl bolus doses up to 20 $\mu g\ kg^{-1}$ and pancuronium 50 $\mu g\ kg^{-1}$. A standard CPB technique was used in all patients. Before aortic cannulation patients were anticoagulated with heparin 375 u. $kg^{-1}$. The bypass circuit consisted of a capillary membrane oxygenator (Maxima/plus, Medtronic, Anaheim, CA, USA) and a roller pump (Stöckert Instruments, Munich, Germany), which was primed with a crystalloid solution.

Patients were allocated randomly to one of four groups: group 1, isoflurane without scavenging system; group 2, desflurane without scavenging system; group 3, isoflurane with scavenging system; and group 4, desflurane with scavenging system. Treatment assignments were contained in sequentially ordered sealed envelopes, which were opened before induction of anaesthesia.

After application of the aortic cross clamp and administration of cold cardioplegic solution, time was allowed to develop a stable level of perfusion pressure and mild hypothermia (32–33 °C). Thereafter volatile anaesthetics were administered during CPB to provide anaesthesia and to control

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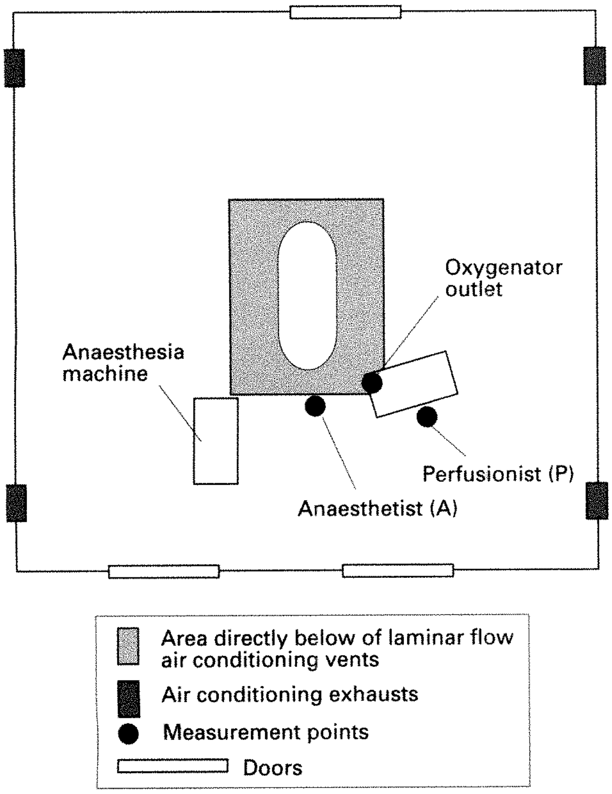

*Figure 1* Ground plan of the operating room with the locations of the measurement points.

arterial pressure, as described previously.[3] The volatile anaesthetics were administered via a vaporizer inserted into the oxygenator gas supply line with a constant gas flow of 3 litre $min^{-1}$. Concentrations were measured using a Datex Capnomac (Helsinki, Finland) at the oxygenator outlet.

### WORKPLACE DESCRIPTION

The oxygenator outlet was connected to the hospital's central scavenging system with a suction flow of 60 litre $min^{-1}$. To avoid negative pressure at the exhaust port of the oxygenator, a hole (0.5 $cm^2$) was placed proximal to the outlet of the oxygenator to provide a pressure balance and avoid malfunction.

The air volume of the operating theatre in this study was 130 $m^3$. Ventilation and air conditioning systems were separate from those serving other rooms of the hospital. Air conditioning was performed by a laminar flow system producing an air exchange rate of 2600 $m^3$ per hour (20 exchanges/hour) without recirculation. The location of the area below the air conditioning vents is shown in figure 1. The exhaust outlets of both the anaesthesia machine and the infrared analyser were connected to the central scavenging system of the hospital.

### DATA ACQUISITION AND ANALYSIS

Measurements of trace concentrations were obtained every 2 min in the breathing zones of the anaesthetist and perfusionist using a highly sensitive direct reading instrument (Bruel and Kjaer 1302, Naerum, Denmark) which is a photoacoustic infrared spectrometry device. The system was calibrated for each substance with trace gas mixtures, for example 15.3 ppm of isoflurane in pure nitrogen. The lower detection limit was 0.01 ppm for both anaesthetics and accuracy was within ±2% over a linear range of 0.01–1000 ppm.

Data acquisition was performed using an IBM compatible computer system (Intel 486 processor, 66 MHz, running under MS-DOS 6.22) and statistical analysis was performed by means of the SPSS for Windows 6.1 software.

Mean trace concentrations were calculated for each anaesthetic from the area under the curves derived from intermittent measurements. Mean concentrations of individual anaesthetics are presented as median (range) for each location and group. Statistical comparisons were made using the Wilcoxon test ($P<0.05$).

## Results

Desflurane was administered in concentrations of 2.6–5.2 vol% and isoflurane at 0.55–1.1 vol% during cardiopulmonary bypass only. Mean bypass times were 87.3 (SEM 11.2) min in group 1, 85.6 (12.5) min in group 2, 80.6 (9.4) min in group 3 and 78.4 (4.07) min in group 4.

Trace concentrations are presented in table 1. Without a scavenging system exposure to desflurane and isoflurane was 3–5 times higher than that with scavenging. Figure 2 shows a typical recording with and without a scavenging system during desflurane anaesthesia. The NIOSH occupational

*Table 1* Median (range) mean trace concentrations of the single measurements. Values are in parts per million (ppm). *$P<0.05$ between "scavenging" and "no scavenging"

| | Group 1 (isoflurane) (no scavenging) | Group 2 (desflurane) (no scavenging) |
|---|---|---|
| Anaesthetist | 0.31 (0.15–2.08) | 0.90 (0.56–6.08) |
| Perfusionist | 0.33 (0.15–2.10) | 0.93 (0.54–6.10) |
| | Group 3 (isoflurane) (scavenging) | Group 4 (desflurane) (scavenging) |
| Anaesthetist | 0.14 (0.13–0.19)* | 0.24 (0.09–0.81)* |
| Perfusionist | 0.16 (0.13–0.20)* | 0.26 (0.10–0.79)* |

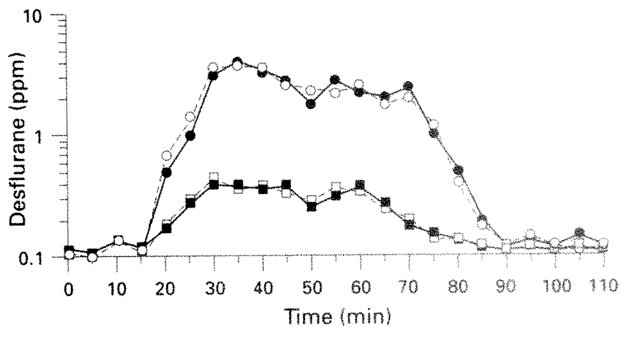

*Figure 2* Example of time-dependent waste gas concentrations of two anaesthetic procedures with identical CPB times. Exposure values for the anaesthetist (■, ●) and perfusionist (□, ○) are indicated as ■, □ (scavenged) and ●, ○ (non-scavenged), respectively.

exposure standard of 2 ppm was exceeded in several cases without using a scavenging system. With a scavenging system, all values were less than 1 ppm.

In general, exposure to desflurane was higher than that to isoflurane, with and without scavenging the membrane oxygenator outlet. However, the differences were not as high as expected from the differences in concentration in the oxygenator. There were no differences in exposure of the anaesthetist or perfusionist.

## Discussion

Volatile anaesthetics are often used during hypothermic cardiopulmonary bypass, because of their vasodilator and anaesthetic properties, to produce unconsciousness and suppression of reflex responses to noxious stimulation.[3] Whereas isoflurane is used routinely, desflurane (difluoromethyl 1-fluoro 2,2,2-trifluoro ethyl ether) has only recently become available for clinical use in the USA and Europe. Desflurane has also been used for cardiac surgery and it appears to have haemodynamic effects similar to those of isoflurane.[4] These substances contaminate operating theatre air, leading to chronic exposure to trace concentrations of inhaled anaesthetics, which may be hazardous to health.[5-8] These suggestions are based mainly on epidemiological studies. The limitations of these studies have been discussed elsewhere.[9-13] Because of flaws in the epidemiological investigations and lack of data on dose relationships, it has not been possible to establish an aetiological connection between untoward health responses and waste anaesthetic gases. However, the potential risk of harmful effects from chronic occupational exposure to gaseous anaesthetics has led to the setting up of occupational exposure standards.

In European countries, recommended occupational exposure standards are specific for individual agents and range from 20 ppm (Germany) to 50 ppm (UK) and are mostly related to an 8-h time-weighted average exposure.[1 2] In contrast, the US National Institute for Occupational Safety and Health (NIOSH) recommends a global occupational exposure standard of 2 ppm for all halogenated agents related to an average over the period of anaesthetic administration.[14] This occupational exposure standard is based mainly on the lowest level detectable using the sampling and analysis techniques recommended by NIOSH in 1977.[14]

As pollution of the operating theatre cannot be prevented in general, health authorities have developed technical procedures (e.g. sampling methods, leak test procedures, medical surveillance and training methods) to keep exposure to waste anaesthetic gases low.

It has been shown recently that under modern working conditions and with respect to these recommendations, occupational exposure to sevoflurane, isoflurane and enflurane can mostly be kept lower than 2 ppm.[15-17]

In this study, waste gas concentrations did not exceed 10 ppm, despite a high leakage of 5 litre $\text{min}^{-1}$ with 0.5–5 vol% (5000–50000 ppm) of volatile anaesthetics. Occupational exposure was low because of an effective air conditioning system with 20 air exchanges per hour. In spite of low concentrations in the working area, this study demonstrated that the use of a scavenging system reduced occupational exposure to volatile anaesthetics further. This may be relevant, particularly in an operating theatre with lower air exchange rates of the air conditioning system.

We therefore recommend routine use of scavenging devices during cardiopulmonary bypass to keep exposure to inhaled anaesthetics low.

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# Effects of chronic β-blockade on compensatory mechanisms during acute isovolaemic haemodilution in patients with coronary artery disease

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## Summary

We have compared compensatory mechanisms during acute isovolaemic haemodilution of 12 ml/kg body weight of blood with hydroxyethyl starch (450 000/0.7) exchange, in non-β-blocked and β-blocked patients with coronary artery disease. During haemodilution, mean concentrations of haemoglobin decreased from 12.8 (SEM 0.2) to 10.1 (0.1) g $dl^{-1}$ ($P<0.01$). Only β-blocked patients had an increase in cardiac index ($P<0.01$); in non-β-blocked patients, cardiac index remained constant. In both groups oxygen extraction increased ($P<0.01$), but the increase tended to be greater in non-β-blocked patients ($P=0.06$). Oxygen consumption was maintained in both groups. There were no ECG signs of myocardial ischaemia. We conclude that β-blocked and non-β-blocked patients with coronary artery disease tolerated well moderate haemodilution to a haemoglobin value of approximately 10 g $dl^{-1}$, however, compensatory haemodynamic mechanisms differed fundamentally between the two groups. (*Br. J. Anaesth.* 1997; **78**: 381–385).

**Key words**
Blood, haemodilution. Surgery, cardiovascular. Heart, coronary artery bypass. Pharmacology, antagonists adrenergic.

Increases in cardiac output and oxygen extraction are the two major compensatory mechanisms during acute isovolaemic haemodilution.[1] The effect of chronic β-adrenergic blocker therapy on these compensatory mechanisms, however, is largely unknown in patients with coronary artery disease.[1]

Acute i.v. β-adrenergic block did not compromise an increase in cardiac output in animals undergoing experimental haemodilution,[2–4] but short-term oral β-adrenergic blocker therapy blunted this compensatory mechanism.[5 6] Conversely, long-term β-adrenergic blocker therapy resulted in an increase in myocardial β-adrenergic receptors[7 8] with a concomitant increase in left ventricular ejection fraction in patients with congestive heart failure.[7 9–11] Chronic β-adrenergic blocker therapy therefore could modify the increase in cardiac output during haemodilution.

We have compared prospectively haemodynamic compensatory mechanisms in patients receiving chronic β-adrenergic blocker therapy and those not receiving β-adrenergic blockers, undergoing coronary artery bypass surgery during preoperative isovolaemic haemodilution.

## Patients and methods

With approval of the local Ethics Committee and written informed consent, over a period of 2 yr we studied 20 consecutive patients not receiving β-adrenergic blocker therapy and 62 chronically β-blocked patients undergoing elective first-time coronary artery bypass graft (CABG) surgery. The chronically β-blocked patients were studied in a variety of different designs but were haemodiluted in the same way as the non-β-blocked patients (see below). These 62 chronically β-blocked patients served as a pool from which patients matched for age and left ventricular ejection fraction were selected for comparison. For each of 20 non-β-blocked patients, two β-blocked patients matched for age and left ventricular ejection fraction were chosen by a person with no other knowledge of patient characteristics. Thus the final groups comprised 20 non-β-blocked and 40 β-blocked patients. Ejection fraction was derived digitally from cineangiography.

Exclusion criteria for β-blocked and non-β-blocked patients were myocardial infarction within 10 days, unstable angina (heparin and nitroglycerin infusions and being cared for in the intensive care unit), concomitant valvular cardiomyopathy, left main coronary artery stenosis of more than 50%, absence of sinus rhythm, presence of left bundle branch block and a preoperative haemoglobin concentration of less than 11 g $dl^{-1}$. Patients were not excluded on the basis of a low ejection fraction or advanced age.

The evening before operation and also on the morning of operation, patients received their regular cardiovascular drugs, including β-blockers (when applicable), calcium entry blockers and nitrates.

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Angiotensin converting enzyme (ACE) inhibitors were not given on the morning of operation corresponding to an institutional practice in patients undergoing CABG surgery. The preoperative β-blocking regimen consisted of atenolol in 27 patients (daily doses of 25 mg in two, 50 mg in 17 and 100 mg in eight patients), metoprolol in eight patients (daily doses of 50 mg in two, 100 mg in one and 200 mg in one patient), bisoprolol (5 mg) in two patients and propranolol (60 mg), bopindolol (1 mg) and celiprolol (200 mg) in one patient each. Patients were premedicated with oral flunitrazepam 1–2 mg, approximately 2 h before induction of anaesthesia.

In the anaesthesia induction area, patients were monitored with pulse oximetry and five-lead ECG, and a peripheral venous cannula and a radial arterial cannula were inserted. Patients were given Ringer's lactate 5 ml $kg^{-1}$. Anaesthesia was induced with fentanyl and midazolam, and neuromuscular block was produced with pancuronium. Anaesthesia was maintained with infusions of fentanyl 0.05 $\mu g\ kg^{-1}\ min^{-1}$ and midazolam 0.75 $\mu g\ kg^{-1}\ min^{-1}$.[12] After tracheal intubation a triple-lumen central venous catheter and a pulmonary artery catheter were inserted via the right internal jugular vein. An additional large gauge (14-gauge) catheter was inserted into a cubital vein of the contralateral arm for future removal of blood. The lungs were ventilated mechanically to normocapnia using an air–oxygen mixture with an inspiratory oxygen concentration of 50% and a ventilatory frequency of 10 bpm.

After baseline measurements, patients were haemodiluted in a two-step procedure. Initially, 6 ml/kg body weight (BW) of blood was removed from the cubital vein and replaced simultaneously and isovolaemically with 6% hydroxyethyl starch over 15–20 min (450 000/0.7) (Plasmasteril, Fresenius AG, Bad Homburg, Germany) according to central venous pressure, that is maintaining central venous pressure stable at each patient's individual level before haemodilution. Thirty minutes after the first measurement, a second set of measurements was performed. An additional 6 ml/kg BWof blood was then exchanged with 6% hydroxyethyl starch (total 12 ml/kg BW) over 15–20 min and a third set of measurements was performed 60 min after the first measurement. During haemodilution no other drugs (apart from fentanyl and midazolam infusions) and no other infusions (apart from 6% hydroxyethyl starch (450 000/0.7)) were administered. All measurements were performed before surgery. Measured variables were: heart rate, systemic and pulmonary artery pressures, central venous pressure, pulmonary capillary wedge pressure, cardiac output measured by thermodilution (10 ml of cold saline injections), arterial and mixed venous blood-gas tensions (BGElectrolytes and IL482 Co-Oximeter, Instrumentation Laboratory, Inc., Lexington, MA, USA), ST segments (J+60 ms[13]) in leads II and V5[14] and rectal temperature. From these variables, cardiac index, systemic and pulmonary vascular resistances, and oxygen delivery, oxygen consumption, oxygen extraction and arteriovenous oxygen difference were computed according to standard formulae.[15]

Changes during haemodilution were compared using repeated measures analysis of variance with Greenhouse–Geisser correction (Superanova 1.11, Abacus Concepts, Inc., Berkeley, CA, USA) followed by paired *t* tests with Bonferroni correction (Statview 4.02, Abacus Concepts, Inc., Berkeley, CA, USA). Patient characteristics and baseline data were compared using unpaired *t* tests and Fisher's exact tests. $P<0.05$ was considered statistically significant. Data are presented as mean (SEM).

## Results

### PREOPERATIVE PATIENT CHARACTERISTICS

Non-β-blocked and β-blocked patients were similar in preoperative characteristics (table 1); the only difference was a lower heart rate in β-blocked patients on the evening before operation. Similar amounts of fentanyl, midazolam and pancuronium were used for induction of anaesthesia in the non-β-blocked and β-blocked patients.

### BASELINE DATA

At baseline, during anaesthesia and immediately before haemodilution, the two groups were very similar (table 2, fig. 1); only PCWP was slightly higher in non-β-blocked patients and the ST segment in lead II was marginally negative in non-β-blocked patients, whereas it was minimally positive in β-blocked patients.

### RESPONSE TO HAEMODILUTION

During haemodilution, haemoglobin concentrations decreased from 12.7 (0.3) to 10.0 (0.3) g $dl^{-1}$ in non-β-blocked patients and from 12.8 (0.2) to 10.1 (0.1) g $dl^{-1}$ in β-blocked patients (table 2). Filling pressures were constant in both groups (table 2). Cardiac index, however, increased only in β-blocked patients whereas in non-β-blocked patients cardiac index remained unchanged during haemodilution (fig. 1A). Oxygen extraction increased in both groups during haemodilution but the increase tended to be greater in non-β-blocked patients ($P=0.06$) (fig. 1B). Correspondingly, a slightly more exaggerated decrease in mixed venous oxygen saturation in non-β-blocked patients ($P=0.05$) was observed (table 2). However, this was not substantiated in (Bonferroni corrected) *post hoc t* tests ($0.025<P<0.05$) (table 2). Oxygen delivery decreased similarly in non-β-blocked and β-blocked patients during haemodilution (table 2). Oxygen consumption was unchanged in non-β-blocked patients and increased minimally in β-blocked patients (table 2). ST segments in lead II were unchanged during haemodilution in both groups. ST segments in lead V5 were unchanged during haemodilution in non-β-blocked patients and became minimally less negative in β-blocked patients (table 2); this was not statistically significant in *post hoc t* tests with Bonferroni correction ($0.025<P<0.05$) (table 2).

Heart rate was generally higher in non-β-blocked patients but decreased in both groups during

*Table 1* Patient characteristics (mean (SEM or range), or percentage or number). LVEF=Left ventricular ejection fraction, NYHA class=functional class (angina) according to the New York Heart Association, MI = myocardial infarction, ACE inhibitors=angiotensin converting enzyme inhibitors. $^*P<0.05$ compared with non—blocked patients

| | Non β-blocked | β-blocked |
|---|---|---|
| Patient characteristics | | |
| Age (yr) | 61 (41–78) | 61 (46–78) |
| Sex (M/F) | 17/3 | 36/4 |
| LVEF (%) | 55 (5) | 57 (3) |
| Body surface area ($m^2$) | 1.9 (0.1) | 1.9 (0.1) |
| NYHA class | 3 median | 3 median |
| Coronary artery disease | | |
| One vessel disease (%) | 0 | 5 |
| Two vessel disease (%) | 35 | 22 5 |
| Three vessel disease (%) | 65 | 72.5 |
| Previous myocardial infarction | | |
| No myocardial infarction (%) | 55 | 37.5 |
| One myocardial infarction (%) | 30 | 40 |
| Two myocardial infarctions (%) | 15 | 20 |
| Three myocardial infarctions (%) | 0 | 2.5 |
| MI within 6 months of operation (%) | 10 | 35 |
| Preoperative drug therapy | | |
| $Ca_{2+}$-channel blockers (%) | 65 | 42.5 |
| ACE inhibitors (%) | 35 | 22.5 |
| Haemodynamics and haemoglobin the day before operation | | |
| Heart rate (beat/min$^{-1}$) | 72 (3) | 60 (1)* |
| Systolic arterial pressure (mm Hg) | 125 (3) | 128 (3) |
| Diastolic arterial pressure (mm Hg) | 79 (2) | 77 (2) |
| Haemoglobin concentration (gm dl$^{-1}$) | 14.0 (0.3) | 14.2 (0.2) |
| Anaesthesia induction | | |
| Fentanyl (μg kg$^{-1}$) | 7.8 (0.7) | 6.9 (0.5) |
| Midazolam (μg kg$^{-1}$) | 97 (8) | 97 (8) |
| Pancuronium (mg kg$^{-1}$) | 0.13 (0.01) | 0.13 (0.01) |

haemodilution (table 2). Stroke volume index increased during haemodilution in both groups (table 2). According to analysis of variance, the increase in stroke volume index was greater in β-blocked patients. In *post hoc t* tests (with Bonferroni correction), this difference, however, was not substantiated ($P=0.028$) (table 2). Mean arterial pressure was unchanged during haemodilution in both groups (table 2). Systemic vascular resistance was unchanged in non-β-blocked patients but decreased during haemodilution in β-blocked patients. Mean pulmonary arterial pressure was

*Table 2* Haemodynamic and pulmonary data during haemodilution in non β-blocked and β-blocked patients. Values are mean (SEM) Hb=Haemoglobin, Temp.=temperature, MAP=mean arterial pressure, MPAP=mean pulmonary artery pressure, CVP=central venous pressure, PCWP=pulmonary capillary wedge pressure, HR=heart rate, SVI=stroke volume index, $AVDO_2$=arteriovenous oxygen difference, ST II=ST segment deviation in lead II, ST V5=ST segment deviation in lead V5, $Pa_{O_2}$=arterial oxygen partial pressure, $Pa_{CO_2}$=arterial carbon dioxide partial pressure, BE=base excess, $HCO_3^-$=bicarbonate concentration, $Sv_{O_2}$=mixed venous haemoglobin saturation, $Do_2I$=oxygen delivery index, $Vo_2I$=oxygen consumption index, SVR=systemic vascular resistance, PVR=pulmonary vascular resistance. †($P<0.05$) at baseline, $^*P<0.05$, (Bonferroni corrected) compared with baseline (intra-group comparison)

| | Non β-blocked | | | β-blocked | | |
|---|---|---|---|---|---|---|
| | Baseline | 6 ml kg$^{-1}$ | 12 ml kg$^{-1}$ | Baseline | 30 min | 60 min |
| Hb (g dl$^{-1}$) | 12.7 (0.3) | 11.3 (0.3)* | 10.0 (0.3)* | 12.8 (0.2) | 11.5 (0.2)* | 10.1 (0.1)* |
| Temp. (°C) | 35.9 (0.1) | 35.6 (0.1)* | 35.4 (0.1)* | 35.9 (0.1) | 35.6 (0.1)* | 35.4 (0 1)* |
| MAP (mm Hg) | 70.1 (1.7) | 68.1 (2.0) | 68.4 (2.1) | 68.8 (1.3) | 67.4 (1.1) | 69 2 (1.2) |
| MPAP (mm Hg) | 16.0 (1.0) | 15.5 (1.0) | 16.0 (1.0) | 14.3 (0.5) | 14.2 (0.5) | 14.9 (0 5)* |
| CVP (mm Hg) | 6.5 (0.5) | 6.2 (0.5) | 6.5 0.5) | 5.9 (0.4) | 5.6 (0.4) | 5.7 (0.4) |
| PCWP (mm Hg) | 8.5 (0.8)† | 7.9 (0.8) | 8.5 (0.8) | 6.3 (0.5) | 6.0 (0.5) | 6.3 (0.5) |
| HR (beat min$^{-1}$) | 62.4 (3.3) | 59.5 (3.2)* | 57.6 (3.1)* | 57.0 (1.5) | 55.3 (1.5)* | 53.9 (1.5)* |
| SVI (ml m$^{-2}$) | 37.3 (1.6) | 39.7 (2.0)* | 40.8 (2.0)* | 37.1 (1.0) | 40.2 (1.1)* | 42.9 (1.1)* |
| $AVDO_2$ (ml dl$^{-1}$) | 4.6 (0.2) | 4.7 (0.2) | 4.5 (0.2) | 4.8 (0.2) | 4.9 (0.2) | 4.5 (0.1)* |
| ST II (mV) | −0.017 (0.010)† | −0.014 (0.009) | −0.010 (0.008) | 0.010 (0.005) | 0.010 (0.005) | 0 011 (0.005) |
| ST V5 (mV) | −0.046 (0.014) | −0.045 (0.014) | −0.044 (0.014) | −0.017 (0.008) | −0.014 (0.008) | −0.014 (0.008) |
| $Pa_{O_2}$ (kPa) | 15.4 (1.1) | 15.9 (1.1) | 17.5 (1.1)* | 14.5 (0.8) | 14.8 (0.8) | 16.6 (0.8)* |
| $Pa_{CO_2}$ (kPa) | 5.3 (0.1) | 5.1 (0 1)* | 5.1 (0.1)* | 5.2 (0.1) | 5.1 (0.1)* | 5.0 (0.1)* |
| pH | 7.43 (0.01) | 7.43 (0.01) | 7.43 (0.01) | 7.43 (0.01) | 7.43 (0.01) | 7.43 (0.01) |
| BE (mmol like$^{-1}$) | 2.6 (0.4) | 2.1 (0.3)* | 1.8 (0.4)* | 2.2 (0.2) | 1.7 (0.2)* | 1.4 (0.2)* |
| $HCO_3^-$ (mmol like$^{-1}$) | 26.4 (0.4) | 25.6 (0.4)* | 25 4 (0.4)* | 26.0 (0.3) | 25.4 (0.2)* | 25.0 (0.3)* |
| $Sv_{O_2}$ (%) | 74.0 (0.9) | 70.7 (1.1)* | 69.0 (1.1)* | 72.5 (0.9) | 69.9 (1.0)* | 69.3 (0.9)* |
| $Do_2I$ (ml min$^{-1}$ m$^{-2}$) | 399 (17) | 356 (14)* | 318 (12)* | 371 (13) | 352 (13)* | 327 (12)* |
| $Vo_2I$ (ml min$^{-1}$ m$^{-2}$) | 103 (4) | 105 (4) | 101 (3) | 99 (3) | 104 (3)* | 101 (3) |
| SVR (dyn s cm$^{-5}$) | 1204 ( 47) | 1159 (47) | 1157 (43) | 1302 (40) | 1227 (41)* | 1208 (41)* |
| PVR (dyn s cm$^{-5}$) | 140 (12) | 141 (11) | 139 (12) | 163 (8) | 161 (8) | 161 (8) |

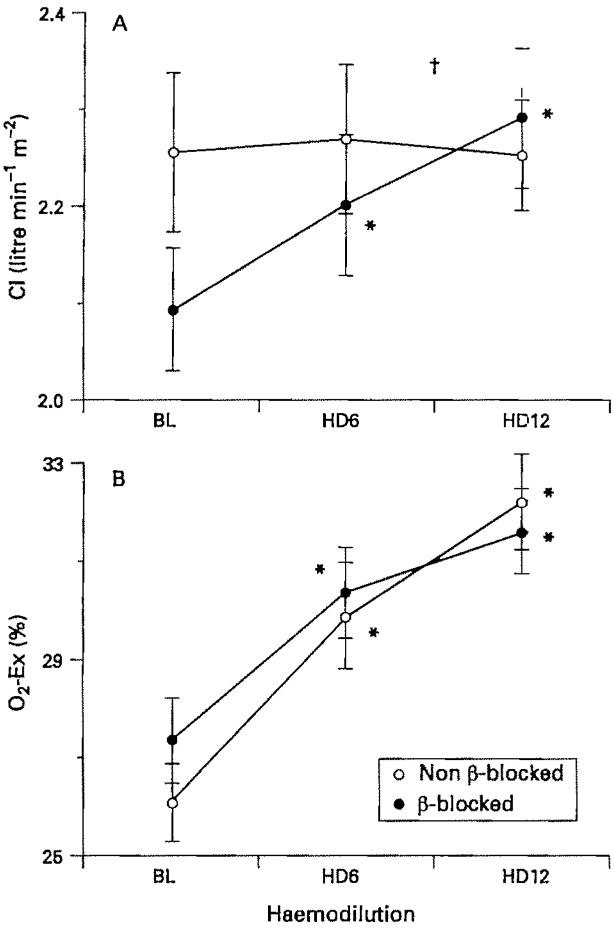

*Figure 1* Changes in cardiac index (CI) (A) and oxygen extraction ($O_2$-Ex) (B) during progressive haemodilution of 6 ml/kg body weight (HD6) and 12 ml/kg body weight (HD12) of blood for hydroxyethyl starch exchange. *$P<0.05$ (Bonferroni corrected) compared with baseline (BL) (intra-group comparison); †$P<0.05$ (Bonferroni corrected) between non-β-blocked and β-blocked patients during haemodilution (between-group comparison).

unchanged during haemodilution in non-β-blocked patients but increased slightly in β-blocked patients (table 2). Pulmonary vascular resistance was unchanged during haemodilution in both groups (table 2).

$Pa_{O_2}$ increased similarly during haemodilution and $Pa_{CO_2}$ decreased slightly in both groups (table 2). Base excess and bicarbonate decreased during haemodilution similarly in both groups. pH was stable during haemodilution in both groups. Arteriovenous oxygen difference was unchanged in non-β-blocked patients but decreased in β-blocked patients during haemodilution (table 2).

## Discussion

We have found that chronically β-blocked and non-β-blocked patients with coronary artery disease tolerated well moderate isovolaemic haemodilution to a haemoglobin concentration of approximately 10 g dl$^{-1}$. However, compensatory haemodynamic responses of chronically β-blocked and non-β-blocked patients differed. While chronically β-blocked patients compensated for acutely lower arterial oxygen content by increases in cardiac index and oxygen extraction, non-β-blocked patients demonstrated an increase in oxygen extraction only and there was no increase in cardiac index.

As short-term oral β-adrenergic blocker therapy reduced the increase in cardiac index in animals undergoing experimental haemodilution,[5 6] a blunted increase in cardiac index might also be expected in chronically β-blocked patients during preoperative haemodilution. However, we observed the opposite, namely an increase in cardiac index exclusively in chronically β-blocked patients whereas cardiac index did not increase during haemodilution in non-β-blocked patients (fig. 1A). This might be because of increased numbers of myocardial β-adrenergic receptors, as observed during long-term β-adrenergic blocker therapy,[7 8] resulting in increased exercise capacity[10] and an exaggerated response to exogenous catecholamines such as dobutamine.[8] As endogenous catecholamines increase during acute isovolaemic haemodilution[16 17] and this is considered an important mechanism for the increase in cardiac index,[1] it is conceivable that after long-term oral β-blocker therapy patients may respond with a greater increase in cardiac index compared with non-β-blocked patients.

Alternative explanations for why non-β-blocked patients responded differently to haemodilution have to be considered. Oral β-blockade is initiated frequently in the medical treatment of coronary artery disease in the referral area of our hospital. Thus non-β-blocked patients might represent a particular selection of patients. In 10 of the 20 non-β-blocked patients studied (50%) a specific reason existed why the referring physician chose not to prescribe oral β-blocker therapy. These reasons were chronic obstructive pulmonary disease (six patients), peripheral arterial occlusive disease (two patients), side effects of β-blocker therapy (one patient) and symptomatic bradycardia before initiation of β-blocker therapy (one patient). In the remaining 10 patients no specific reason was found in the medical history why oral β-blocker therapy had not been given. Left ventricular ejection fraction was *not* lower in these patients without a clear reason for not being β-blocked (57.6 (6.3) %) compared with patients with a reason (52.8 (7.5) %). Conversely, most patient characteristics and baseline data were similar in non-β-blocked and β-blocked patients. The only differences were a lower heart rate on the evening before CABG surgery in β-blocked patients (table 1), a slightly higher PCWP at baseline, that is immediately before haemodilution (table 2) and a slightly negative ST segment in ECG lead II at baseline (table 2). The lower heart rate and the lower PCWP are caused by long-term β-blocker therapy.[8 9 18] The effect of a slightly negative ST segment in ECG lead II at baseline in non-β-blocked patients compared with a slightly positive ST segment in this lead in β-blocked patients (table 2) on the differential response during haemodilution is difficult to judge. However, because the slightly negative ST segment in ECG lead II in non-β-blocked patients became minimally but significantly *less* negative during haemodilution, myocardial ischaemia induced by haemodilution in non-β-blocked patients is not a likely reason to explain the lack of increase in cardiac index during haemodilution. Also, the trend towards a higher incidence of myocardial infarction within 6 months before operation in the β-blocked patients (table 1) is not a likely reason for why these patients had an increase in cardiac output during haemodilution compared with non-β-blocked patients with a slightly lower incidence of recent myocardial infarction. Thus we consider such alternative explanations for the different response of non-β-blocked and β-blocked patients as relatively unlikely.

We did not observe ECG alterations suggestive of myocardial ischaemia in any patient (new ST depression >0.1 mV or a new ST elevation >0.2 mV[13]). However, the combined sensitivity of leads II and V5 to detect intraoperative myocardial ischaemia is only approximately 80%.[14] Thus there is a possibility that undetected myocardial ischaemia might have developed during haemodilution. This is unlikely because of the absence of secondary manifestations of ischaemia, such as cardiac arrhythmias, increases in PCWP or decreases in arterial pressure or cardiac index.[19]

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# Perioperative myocardial cell injury: the role of troponins

H. METZLER, M. GRIES, P. REHAK, TH. LANG, S. FRUHWALD AND W. TOLLER

## Summary

Early recognition of minor myocardial cell injury and appropriate treatment may prevent development of myocardial infarction as one of the most severe postoperative cardiac complications. Troponins have been shown to be sensitive biochemical markers for the assessment of myocardial cell injury. We investigated prospectively 67 cardiac risk patients undergoing elective non-cardiac surgery. Troponin T (TNT) concentrations were measured during the perioperative period, and in those patients with increased TNT (cut-off 0.2 ng ml$^{-1}$), troponin I (TNI) concentrations were measured additionally (cut-off 0.6 ng ml$^{-1}$). Patients were allocated to one of three groups: group I, all patients with normal TNT concentrations had a good cardiac outcome (80.5%). In those patients with increased TNT concentrations (19.5%) TNI was also positive; group II, patients (8.8%) with only slightly increased TNT concentrations (0.32–0.99 ng ml$^{-1}$) also had a good outcome, indicating minor myocardial cell injury, whereas patients with cardiac complications (11.9%) had higher TNT concentrations (0.47–9.8 ng ml$^{-1}$) ($P<0.05$) (group III). With a TNT cut-off at 0.2 ng ml$^{-1}$, the positive predictive value for adverse outcome was 61.5%; the negative predictive value was 100%. With a TNT cut-off at 0.6 ng ml$^{-1}$, the positive predictive value for adverse outcome increased to 87.5%, but the negative predictive value was still high (98%). Most of the patients showed an increase in TNT content from the day of surgery until the third postoperative day. We conclude that serial troponin measurements during the perioperative period identify pre-, intra- and postoperative myocardial cell injury. The concentration of troponin T may reflect the degree of injury and help categorize the subsequent risk. (*Br. J. Anaesth.* 1997; **78**: 386–390).

**Key words**
Surgery, non-cardiac. Surgery, perioperative period. Complications, morbidity. Heart, troponins.

Recently, in cardiac risk patients undergoing non-cardiac surgery, a complete perioperative pattern of myocardial ischaemia has been identified.[1–7] Postoperative ischaemia appears to correlate with adverse outcome, and prolonged subendocardial ischaemia rather than acute coronary artery occlusion precedes cardiac complications.[1 2] Perioperative myocardial infarction (MI) represents the most severe complication at the end of an adverse cascade, usually initiated by episodes of myocardial ischaemia which may occur as a reversible or irreversible event. The gap between reversible myocardial ischaemia and definite death of myocardial cells of a major area may be linked by appropriate assessment of minor myocardial cell injury, which may help to prevent MI.

Cardiac troponins have been established as sensitive markers for detection of major and minor myocardial cell injury, avoiding the high incidence of false positive results associated with the use of CK-MB.[8–13] Both troponin T (TNT) and troponin I (TNI) are currently used. TNT has the advantage of a broad diagnostic window of up to 14 days and has been shown to be a marker for minor myocardial cell damage. TNI is expressed exclusively in the myocardium of adults and is highly specific for myocardial cell injury, excluding skeletal muscle damage. To date there have been no studies evaluating myocardial cell injury in the perioperative period using both troponins.

This study was designed to assess the extent of minor myocardial cell injury in cardiac risk patients undergoing elective non-cardiac surgery. The aims of the study were to examine the perioperative pattern of changes in troponin from the day before surgery until the fifth day after operation, to compare TNT and TNI concentrations in those patients with increased TNT concentrations and to compare the positive and negative predictive values of troponin T for adverse outcome.

## Patients and methods

After obtaining approval from the Ethics Committee of the University and informed consent, we investigated prospectively 70 cardiac risk patients undergoing elective non-cardiac surgery. Subjects were included in the study according to the presence of definite or at-risk coronary artery disease (CAD). Definite CAD was defined as previous MI, typical or atypical angina with positive exercise testing or scintigraphic evidence, or previous CABG or PTCA.

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Patients at-risk for CAD were included if they had at least three of the following cardiac risk factors: age >65 yr, hypertension, current smoker, treated diabetes mellitus (insulin or oral hypoglycaemic agents), increased serum cholesterol concentration (>5.7 mmol $litre^{-1}$) or previous vascular surgery.

Before operation, patients were clinically evaluated; this included 12-lead ECG, chest x-ray and echocardiography. Premedication, anaesthesia and postoperative care were performed by clinicians not involved in the study and blinded to all research information. Twelve-lead ECG recordings were performed daily in the morning together with blood sampling (TNT, TNI, CK-MB) from the day before surgery until the fifth postoperative day.

### TROPONIN T ASSAY

Serum TNT was measured using an enzyme-linked immunosorbent assay with the Enzyme-Test-System ES 300 analyser (Boehringer Mannheim, Mannheim, Germany). The method is based on a single step sandwich principle with streptavidin-coated tubes as the solid phase and two monoclonal anti-human cardiac TNT antibodies. Values greater than or equal to 0.2 ng $ml^{-1}$ were considered positive.[13 14]

### TROPONIN I ASSAY

Serum cardiac TNI concentrations were measured using the Stratus Cardiac Troponin-I assay (Dade International Inc. Miami, FL, USA). This is a two-site immunoassay which uses two monoclonal antibodies that are specific for the cardiac isotype of TNI. Values greater than or equal to 0.6 ng $ml^{-1}$ were considered positive.[15]

### CK-MB ASSAY

Photometric determination of the activity of creatine kinase MB-isoenzyme (CK-MB) (*N*-acetylcysteine-activated) on an immunological basis (Granu Test 25, Merck, Darmstadt, Germany) was used. The reference range was ≤12 iu $litre^{-1}$ at 25 °C.

### ADVERSE CARDIAC OUTCOME

An adverse cardiac outcome was defined as the occurrence of unstable angina, severe cardiac arrhythmias compromising cardiovascular status, decompensated congestive heart failure (CHF), MI or cardiac death. MI was diagnosed using the following criteria: CK-MB >12 iu $litre^{-1}$ and electrocardiographic changes, that is development of either new Q-waves or persistent ST-elevation in the 12-lead ECG.

### STATISTICAL ANALYSIS

For comparison of patient groups with good and adverse outcomes the non-parametric Mann–Whitney test was used. $P<0.05$ was considered statistically significant. Changes in the TNI:TNT ratio were analysed by Friedman non-parametric two-way ANOVA.

## Results

Clinical data are summarized in table 1. Three patients were excluded because of incomplete samples for TNT or TNI analysis; 67 patients had complete 7-day profiles, with 469 single TNT samples and 91 TNI samples.

Of these 67 patients, 54 (80.5%) had normal and 13 (19.5%) had increased TNT concentrations, at least at one measurement. The times at which TNT were increased most frequently were on days 2, 3 and 4 after operation. No patient had increased TNT concentrations 24 h before operation, but two patients had increased concentrations on the morning of surgery.

Nine patients were still TNT positive at the end of the study (fig. 1). Most frequently, the first increase in TNT concentrations above the cut-off value were noted on the first and second postoperative days; two patients however, had a relatively late increase in TNT concentrations on day 4 after operation (fig. 2). Of the two patients with increased TNT concentrations

*Table 1* Clinical data for the 67 patients

| | No. of Patients (%) |
|---|---|
| Age <65 yr | 46 (69) |
| Sex (M/F) | 50/17 (74/25) |
| Hypertension | 47 (70) |
| Diabetes mellitus | 9 (13) |
| Current smoking | 37 (55) |
| Increased cholesterol | 61 (91) |
| Cardiac history | |
| Angina pectoris | 61 (91) |
| Unstable angina | 6 (9) |
| Previous MI | 43 (64) |
| History of congestive HF | 11 (16) |
| Previous CABG | 7 (10) |
| Previous PTCA | 13 (19) |
| Preoperative cardiac medication | |
| Nitrates | 44 (66) |
| Calcium antagonists | 24 (36) |
| β-adrenergic blockers | 9 (13) |
| Digoxin | 22 (33) |
| ACE inhibitors | 22 (33) |
| Type of surgery | |
| Vascular | 38 (56,7) |
| Abdominal | 21 (31,3) |
| Orthopaedic | 8 (12) |
| Type of anaesthesia | |
| General | 63 (94) |
| Regional | 4 (6) |

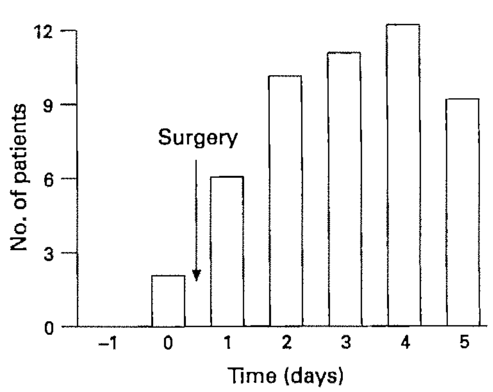

*Figure 1* Number of patients with increased TNT concentrations at different measurement times.

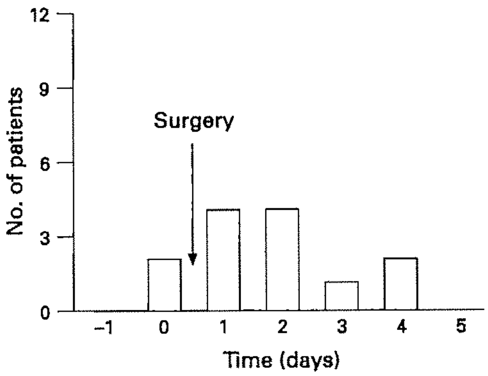

*Figure 2* Time when TNT concentrations first increased above the cut-off values.

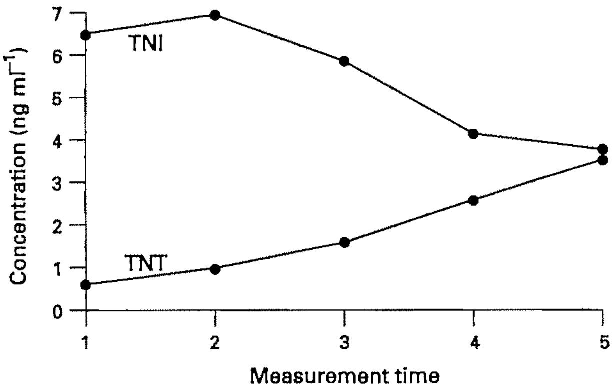

*Figure 3* Mean TNT and TNI concentrations for all patients with increased concentrations of TNT. Measurement times are numbered from the first above the cut-off value.

before operation, one developed CHF after operation. Of the six patients with an increase in TNT on the morning after surgery, four had intraoperative problems such as tachycardia, hypotension or hypertension. Two developed CHF immediately after surgery.

In all 13 patients with increased TNT concentrations, TNI concentrations were also above the cut-off value, although the pattern was different (fig. 3). Individual ratios for TNI:TNT decreased significantly from a mean value of 8.8 to 1.1 ($P<0.01$).

All patients with normal TNT concentrations had a good outcome (80.5%), except for one patient who died because of sudden severe bleeding from the femoral artery on day 10 after operation. In five patients (7.5%) TNT was positive, although there were no cardiac complications. All except one patient, however, had relatively low TNT values (<0.06, 0.32–0.99 ng ml$^{-1}$). Eight of the 13 patients (11.9%) with increased TNT concentrations (0.47–9.8 ng ml$^{-1}$) had an adverse outcome: three patients suffered from unstable angina, in three patients congestive heart failure occurred, one patient developed malignant arrhythmias and another postoperative non-Q-wave infarction. All eight patients had relatively high TNT values (fig. 4). The difference between groups 2 and 3 was significant ($P<0.05$). With a cut- off value for TNT of 0.2 ng ml$^{-1}$, the positive predictive value for adverse outcome was 61% and the negative predictive value was 100%. With a change in the cut-off to 0.6 ng ml$^{-1}$, the positive predictive value improved to 87%, but the negative predictive value was still high (98%).

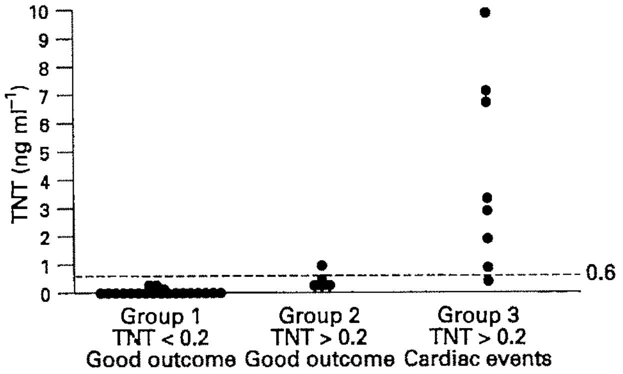

*Figure 4* TNT concentrations in relation to outcome.

A total of 76.9% of the patients with positive TNT values underwent vascular surgical procedures, although this subgroup represented only 56.7% of the total patient population. In contrast, the orthopaedic subgroup, representing 14%, demonstrated no increases in TNT.

There were no significant differences in patient characteristics between those with and without adverse outcomes or with and without increased TNT concentrations.

CK-MB was positive in 14 patients. Three patients had increased CK-MB concentrations, although both TNT and TNI were negative, and four patients had normal CK-MB concentrations, although both troponins were positive. By defining myocardial cell injury as an event with an increase in troponin T and I, the sensitivity of CK-MB was 70% and specificity was 94%. With the exception of one patient with preoperative renal insufficiency (creatinine 4.4 mg/100 ml) and constant high CK-MB concentrations of approximately 500 iu litre$^{-1}$, CK-MB concentrations were increased only for a short time, most often only 24 h.

Seven patients with increased TNT concentrations had transient ST-segment depression on the daily 12-lead ECG and one patient with MI showed ST-segment elevation. Three patients with an increase in troponin T concentrations did not show an increase in CK-MB or electrocardiographic changes.

## Discussion

The primary goal of postoperative biochemical monitoring of cardiac risk patients is to establish appropriate markers in order to detect early minor myocardial cell injury, to inhibit postoperative MI as one of the most threatening cardiac events and to exclude the existence of cardiac complications. Landesberg, Luria and Cotev demonstrated in major vascular surgery patients that cumulative prolonged subendocardial ischaemic events rather than shorter ischaemic periods are followed by cardiac complications.[2] Postoperative electrocardiographic ST-segment changes, however, indicate myocardial ischaemia which may or may not be followed by definite cell injury and require continuous ECG Holter monitoring.

Troponins have been introduced as sensitive biochemical markers of myocardial cell injury, both in medical patients and also in the postoperative period.[9 12 16] Katus, Schoeppenthau and Tanzeem were the first to study TNT concentrations after cardiac and non-cardiac surgery.[16] Adams, Sigard and Allen used TNI as a sensitive and specific method for the diagnosis of perioperative MI.[9] In the study of Lee, Thomas and Ludwig, increases in TNT were associated not only with MI but also with other major cardiac complications in patients without definite MI.[12] The results of our study allowed discrimination between three perioperative risk groups based on concentrations of troponin. No patient with TNT within the normal range had cardiac complications (group 1) and seven of eight patients with significantly increased values (group 3) suffered cardiac events. Between these two groups we found patients with only slightly increased TNT concentrations but without cardiac events, possibly resulting from minor, reversible myocardial cell injury. The cut-off in this series could be drawn at a concentration of 0.6 ng $ml^{-1}$ with only one false positive (group 2) and one false negative (group 3) result in each group. For our study population the higher cut-off value of 0.6 ng $ml^{-1}$ for troponin T appeared to better predict adverse outcome compared with 0.2 ng $ml^{-1}$.

The prolonged duration of our study (over 7 days), including the 24 h before surgery, allowed complete analysis of the beginning of cell damage. Although most of the injury occurred in the period from the day of surgery until the third postoperative day, two patients had a "late injury" profile, with normal TNT concentrations until day 3 after operation day and then an increase on day 4.

Two troponins are currently recommended for the diagnosis of myocardial cell injury. Increases in TNI concentrations are highly specific.[17 18] In contrast with TNT, TNI is not expressed in skeletal muscle throughout ontogeny.[17 18] TNT is a slightly larger protein than TNI and it has been used to stratify patients into high and low risk categories based on detection of minor myocardial cell damage.[14] Studies have demonstrated that in contrast with TNT or CK-MB, increases in TNI do not occur in acute or chronic muscle disease.[18 19] Cross- reactivity between cardiac and skeletal TNT appears to be 1–3% and may be decreased when specific monoclonal antibodies are used.

Therefore, we measured both troponins in those patients with increased TNT concentrations. Identical trends in TNT and TNI should exclude the probability of increases in TNT of non-cardiac origin. In this study, all patients with increased TNT concentrations also had positive TNI values. TNI reached the highest mean values at the first two measurement times and decreased afterwards, whereas mean TNT values increased gradually with the highest values at the fifth measurement time. We cannot account for this difference as there have been no studies comparing TNT and TNI trends in minor myocardial cell injury. The TNT and TNI content of the free cytoplasmic pool may differ. TNT has a higher molecular weight than TNI (33 000 *vs* 23 500 Da). Therefore, different release or clearance kinetic profiles, or both, may be responsible for this difference.

In addition to skeletal muscle injury, increases in TNT without a concomitant increase in TNI may be caused by renal disease.[20 21] In a recent study, Bhayana, Gougoulias and Cohoe demonstrated differences between results for TNT and TNI in renal patients.[20] They hypothesized three possible mechanisms: cross-reactivity of the assay, skeletal muscle gene expression of cardiac TNT or minimal cardiac damage. One patient in our study with preoperative renal insufficiency and constant increases in CK-MB showed a transient increase, but of both troponins.

The disadvantage of CK-MB as a biochemical marker of perioperative myocardial cell injury compared with troponins is not only its lower sensitivity and specificity but also the short diagnostic window of approximately 24 h.

## Acknowledgement

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*British Journal of Anaesthesia* 1997; 78: 391–395

# A study of the anatomy of the caudal space using magnetic resonance imaging

I. M. CRIGHTON, B. P. BARRY AND G. J. HOBBS

## Summary

We have studied, in 37 adult patients, the anatomy of the sacral extradural (caudal) space using magnetic resonance imaging The sacrococcygeal membrane (SCM) could not be detected in 10.8% of patients. The maximum depth of the caudal space adjacent to the SCM was beneath the upper third of the SCM in more than 90% of patients (mean depth 4.6 mm; range 1.0–8.0 mm). The shortest linear distance from the dura to the upper limit of the SCM varied considerably (60.5 mm; 34–80 mm) as did the volume of the caudal space excluding the foraminae and dural sac (14.4 $cm^3$; 9.5–26.6 $cm^3$). The dimensions of the caudal space and their variability have implications for clinical practice and a knowledge of these dimensions may increase both the reliability and safety of caudal techniques in adult patients. (*Br. J. Anaesth.* 1997; **78**: 391–395).

**Key words**
Anatomy, extradural space. Anaesthetic techniques, extradural. Measurement techniques, magnetic resonance imaging.

The caudal approach to the extradural space (caudal block) is used for intraoperative and postoperative analgesia for a variety of operations and for the management of chronic pain. The sacral hiatus marks the termination of the sacral canal and results from failure of fusion of the laminae of the fifth sacral vertebra. To perform a caudal block, the sacral hiatus must first be located and a needle passed through the sacrococcygeal membrane (SCM). This can be difficult or impossible at times because of wide anatomical variation in this region. A detailed understanding of the anatomy of the caudal region of the extradural space is therefore desirable for clinicians using this technique.

Current anatomical knowledge of this region is based largely on post-mortem studies from more than 50 yr ago. These were performed after a revival of interest in continuous caudal analgesia in obstetric practice.[1] In the same decade, the "recent" and skeletonized sacral anatomy of cadavers was studied[2] and the significance of variations in sacral anatomy for the use of caudal analgesia was discussed.[3] However, cadaveric dissection is subject to distortion and measurements may alter after skeletonization of the cadaver.[2] Furthermore, there have been anatomical changes in populations over the past 50 yr.

Recently, other anatomical areas such as the lumbar extradural region have been studied in life using magnetic resonance (MR) imaging.[4] The purpose of our study was to examine the normal anatomy of the sacral extradural (caudal) space in adults using MR imaging.

## Patients and methods

The study was carried out in the MR imaging suite at University Hospital, Nottingham. After a pilot study of 15 patients for familiarization and confirmation of the reproducibility of measurements, the anatomy of the caudal space relevant to the performance of caudal block was studied prospectively using MR images of 37 adult patients presenting for primary investigation of back pain. MR imaging was part of their routine investigation and no patient had evidence of congenital abnormalities such as spina bifida or a history of spinal surgery.

Patient height, weight and sex were recorded. MR imaging was performed with a Siemens Vision scanner operating at 1.5 T (tesla) with the patient supine. A phased array spine coil was used. The relevant anatomy was demonstrated most clearly using T2 sagittal plane images and consecutive T2 sagittal images of 0.44 cm thickness of the sacrum from the upper margin of S1 to the caudad limit of the sacral hiatus were therefore used (fig. 1). Using the Siemens computer software, measurements were made by two of the authors (I. M. C. and B. P. B.) using stored images for each patient on two separate occasions. If there was a discrepancy between measurements, a third measurement was made and the mean value recorded.

The length (fig. 2) and thickness (fig. 3) of the SCM (if present) were measured on the images giving the largest measurement. Only that part of the SCM through which the sacral canal could be entered with a needle, that is the length of the SCM with clearly visible underlying caudal space, was

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Current anatomical knowledge of this region is based largely on post-mortem studies from more than 50 yr ago. These were performed after a revival of interest in continuous caudal analgesia in obstetric practice.[1] In the same decade, the "recent" and skeletonized sacral anatomy of cadavers was studied[2] and the significance of variations in sacral anatomy for the use of caudal analgesia was discussed.[3] However, cadaveric dissection is subject to distortion and measurements may alter after skeletonization of the cadaver.[2] Furthermore, there have been anatomical changes in populations over the past 50 yr.

Recently, other anatomical areas such as the lumbar extradural region have been studied in life using magnetic resonance (MR) imaging.[4] The purpose of our study was to examine the normal anatomy of the sacral extradural (caudal) space in adults using MR imaging.

## Patients and methods

The study was carried out in the MR imaging suite at University Hospital, Nottingham. After a pilot study of 15 patients for familiarization and confirmation of the reproducibility of measurements, the anatomy of the caudal space relevant to the performance of caudal block was studied prospectively using MR images of 37 adult patients presenting for primary investigation of back pain. MR imaging was part of their routine investigation and no patient had evidence of congenital abnormalities such as spina bifida or a history of spinal surgery.

Patient height, weight and sex were recorded. MR imaging was performed with a Siemens Vision scanner operating at 1.5 T (tesla) with the patient supine. A phased array spine coil was used. The relevant anatomy was demonstrated most clearly using T2 sagittal plane images and consecutive T2 sagittal images of 0.44 cm thickness of the sacrum from the upper margin of S1 to the caudad limit of the sacral hiatus were therefore used (fig. 1). Using the Siemens computer software, measurements were made by two of the authors (I. M. C. and B. P. B.) using stored images for each patient on two separate occasions. If there was a discrepancy between measurements, a third measurement was made and the mean value recorded.

The length (fig. 2) and thickness (fig. 3) of the SCM (if present) were measured on the images giving the largest measurement. Only that part of the SCM through which the sacral canal could be entered with a needle, that is the length of the SCM with clearly visible underlying caudal space, was

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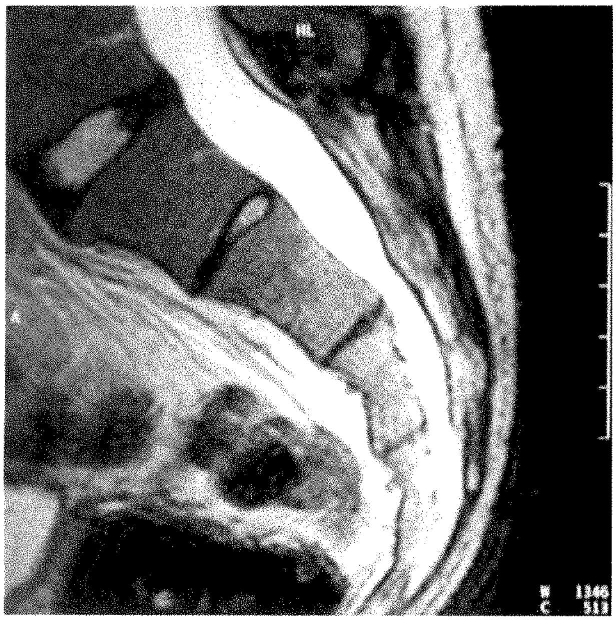

*Figure 1* T2 sagittal image of the sacrum and caudal space.

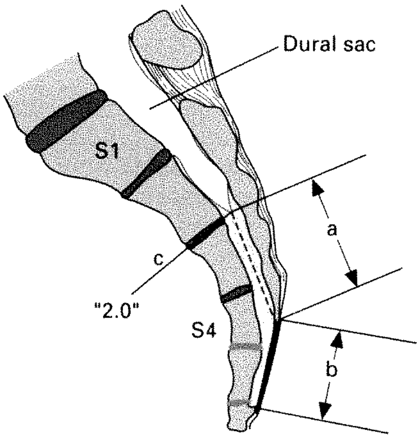

*Figure 2* Diagram of the sacrum and caudal space (using fig. 1 as a template) showing the shortest linear distance from the dura to the upper limit of the sacrococcygeal membrane (a), the length of the sacrococcygeal membrane (b) and the vertebral level of the caudal limit of the dura ("2.0", c).

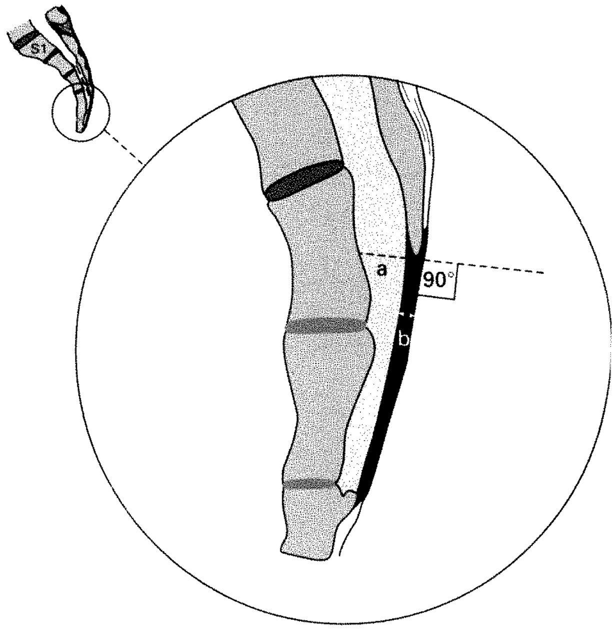

*Figure 3* Diagram of the sacrum and caudal space (using fig. 1 as a template) showing the maximum depth of the caudal space at 90° and adjacent to the sacrococcygeal membrane ("AP diameter", a) and the maximum width of the sacrococcygeal membrane (b).

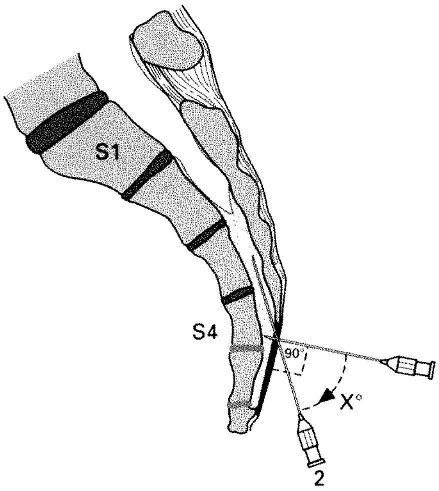

*Figure 4* Diagram of the best fit angle for needle insertion into the caudal space ($X^0$=angle of caudal depression of the needle from position 1 to position 2).

used for these measurements. The location of the upper limit of the SCM (corresponding to the apex of the sacral hiatus) in relation to the adjacent vertebral body was recorded. For example, "4.2" indicated that the upper limit of the SCM was adjacent to a position 4.2 vertebral bodies below the upper margin of the body of S1 (fig. 2). The maximum depth (AP diameter, fig. 3) of the caudal space at an angle of 90° to the SCM and its location in relation to the SCM (upper or middle third of the SCM) were also recorded. The best fit angle for needle insertion into the caudal space via the upper third of the SCM was determined (fig. 4). This position was described by measuring the angle of caudal depression required from a line drawn at 90° to the SCM. The location of the lowest limit of the dural sac in relation to the adjacent vertebral body (as above) and the shortest linear distance from the dura to the upper limit of the SCM were recorded (fig. 2). The volume of the sacral canal excluding the foraminae and the dural sac was estimated by obtaining the product of the sum of the areas of the sacral canal from each T2 sagittal plane image and 0.44 (thickness of each consecutive T2 sagittal image).

Data were analysed where appropriate using Student's *t* test and regression analysis. A probability of 0.05 or less was considered statistically significant.

## Results

We studied 23 females and 14 males (table 1). In one patient, height and weight were not recorded. In two patients the volume of the sacral canal could not be recorded because of poor reproducibility of results. Data from these patients were excluded from appropriate analyses. There were significant differences between the heights and weights of females

*Table 1* Patient data (mean (SD) [range])

| | Females<br>($n$=23) | Males<br>($n$=14) | Combined<br>($n$=37) |
|---|---|---|---|
| Age (yr) | 47 [16–69] | 39 [18–68] | 44 [16–69] |
| Height (cm) | 163.1 (6.7) [150–182] | 176.2 (8.2) [152–183]<br>($n$=13) | 167.8 (9.6) [150–183]<br>($n$=36) |
| Weight (kg) | 64.6 (10.1) [49–91] | 85.6 (18) [60–120]<br>($n$=13) | 72.2 (16.7) [49–120]<br>($n$=36) |

*Table 2* Measurements from MR images (mean (SD) [range] unless otherwise indicated)

| | Females<br>($n$=23) | Males<br>($n$=14) | Combined<br>($n$=37) |
|---|---|---|---|
| Sacrococcygeal membrane (SCM) | | | |
| Absent ($n$ (%)) | 1 (4.3) | 3 (21.4) | 4 (10.8) |
| Upper limit; sacral vertebra (median) | 4.0 [3.2–4.7] | 4.3 [3.4–5.3] | 4.1 [3.2–5.3] |
| Length (mm) | 22.6 (6.8) [13–36] | 22.8 (6.9) [11–31] | 22.6 (6.7) [11–36] |
| Thickness (mm) | 3.6 (1) [1–5] | 2.5 (0.9) [1–4] | 3.2 (1.1) [1–5] |
| Sacral canal | | | |
| Maximum AP diameter at 90° to SCM (mm) | 5 (2.1) [2–8] | 3.8 (1.5) [1–6] | 4.6 (2) [1–8] |
| Location of maximum AP diameter beneath SCM ($n$ (%)) | | | |
| Upper third of SCM | 21 (95.5) | 10 (90.9) | 31 (93.9) |
| Middle third of SCM | 1 (4.5) | 1 (9.1) | 2 (6.1) |
| Best fit angle into sacral canal via SCM (°) | 56.6 (8.9) [40–74] | 60.4 (5.9) [50–68] | 57.9 (8.1) [40–74] |
| Volume (excluding foraminae and dural sac) ($cm^3$) | 13.2 (2.68) [9.5–20]<br>($n$=22) | 16.5 (4.08) [10.8–26.6]<br>($n$=13) | 14.4 (3.59) [9.5–26.6]<br>($n$=36) |
| Dural sac | | | |
| Lowest limit; sacral vertebra (median) | 1.3 [0.8–2.0] | 1.5 [0.9–3.0] | 1.4 [0.8–3.0] |
| Shortest distance (linear) from SCM to dural sac (mm) | 58.5 (13) [34–80] | 64.6 (12.8) [41–78] | 60.5 (13.1) [34–80] |

and males ($P$=0.001 and $P$<0.001, respectively). Table 2 gives the measurements of the SCM, sacral canal and position of the lower limit of the dural sac. Data were comparable for females and males except that the SCM was significantly thicker in females ($P$=0.005) and the volume of the sacral canal was significantly greater in males (16.5 *vs* 13.2 $cm^3$) ($P$=0.019). The relationships between sacral canal volume and height and sacral canal volume and weight are given by the regression equations: $y=-17.7+0.19x$ ($r^2=0.27$, $P=0.002$) and $y=5.76+0.12x$ ($r^2=0.33$, $P<0.001$), respectively. There was no relationship between age and sacral canal volume ($y=17.1-0.06x$, $r^2=0.07$, $P=0.142$).

## Discussion

Successful performance of a caudal block requires identification of the sacral hiatus, passage of a needle through the SCM and placement of the needle (or cannula) along the axis of the sacral canal without entering the dural sac or other structures. This may be technically difficult in adult patients. A detailed knowledge of the anatomy, dimensions and variations of the sacral region are therefore desirable to increase the reliability and safety of using this technique. This knowledge is based mainly on the results of post-mortem studies performed more than 50 yr ago. We were particularly interested to compare our findings with this previous work. Although the patients included in our study presented for investigation of back pain, most of their symptoms originated from the lumbar region of the spine and none had undergone previous spinal surgery or had evidence of a congenital abnormality. We therefore assumed that the anatomy of their sacral region would be representative of the general population.

In 33 patients the SCM was identified easily and measured. However, we were unable to identify a sacral hiatus and SCM on the MR scans in four (10.8%) of our patients. Although we cannot be certain of its absence without axial imaging, in most patients this would represent a clinically insurmountable obstacle when performing a caudal block. Although Trotter and Lanier found obliteration of the hiatus in some of the skeletons in their study, the incidence was not recorded.[5]

Trotter and Lanier[5] located the apex of the hiatus most commonly at the level of the lower third of the body of S4, although this varied greatly. We found the median and mode of the upper limit of the SCM to be at the level of the upper third of the body of S5, although there was also wide variation across two vertebral bodies. It would have been desirable to relate the site of the SCM to a palpable bony landmark such as the tip of the coccyx. However, the tip of the coccyx was not demonstrated clearly in many scans for technical reasons. Identification of other useful and palpable landmarks was also difficult as MR imaging was performed only in the sagittal plane. Our initial evaluation of axial imaging suggested that it added little to the information gained from the sagittal sections.

The mean length of the SCM in our study was

22.6 mm. This measurement was similar to the mean length of 26.3 mm obtained from a study of the "recent" anatomy of approximately 50 cadavers.[2] However, the upper ranges for the bony length of the sacral hiatus for males and females (60 and 65 mm, respectively), as measured by Trotter and Lanier in the sacra of 518 white Americans[5], were larger than for our males and females (31 and 36 mm, respectively). This may be related to our smaller sample size, measurement errors, population differences and almost certainly differences between living and post-mortem tissues.

The mean maximum AP diameter of the caudal space adjacent to the SCM for all of our patients was 4.6 mm. Trotter and Lanier found the mean maximum AP diameter to be 4.6 (SD 1.7; range 0–10) mm and 4.9 (1.5; 0–12) mm in white females and males, respectively.[5] These measurements were similar to our results, although we measured the AP diameter at an angle of 90° to the SCM. This small dimension may contribute to the anatomical difficulties encountered during caudal techniques. Also, Trotter and Lanier found that in 5% of subjects the AP diameter of the canal at the apex of the hiatus was <2 mm. We found only one patient with a diameter of less than 2 mm. Our female patients demonstrated a trend towards larger AP canal diameters ($P=0.078$). This latter observation may suggest that caudal techniques might be performed with less difficulty in female patients, although any differences are probably not clinically relevant. As the maximum canal diameter was found adjacent to the upper third of the SCM in most of our patients (95.5%), passage of a needle near the apex of the SCM might be expected to reduce difficulty in clinical practice.

A common technique for performing a caudal block is to insert the needle at an angle of 90° to the SCM until the ligament is penetrated, followed by depression of the needle until it is estimated that the shaft of the needle is in the plane of the sacral canal and then advancement along the canal.[6] Given the wide variation in sacral anatomy, it is understandably easy to misplace the needle in adults. Our findings suggest that successful needle placement is more likely if the needle is inserted at 90° to the SCM and then depressed in a caudal direction through an angle of approximately 55–60°. However, the variation in this angle must be taken into account.

Early anatomical studies suggested that the volume of the sacral canal (including the sacral foraminae) in adults was slightly more than 30 (range 12–65) ml.[7] However, this is the volume of dry bones and in life the canal is filled with the dural sac and its contents, nerves, blood vessels, fat and connective tissue. We estimated the mean volume of the sacral canal to be 14.4 (range 9.5–26.6) cm$^3$, a much smaller volume than that reported previously. This could be explained partly by our measurement not including the volume of the dural contents or the volume of the sacral foraminae. Relating our measurement of canal volume to clinical practice is difficult. However, when making clinical decisions as to the injectate volume necessary for particular caudal techniques, it should be noted that previous radio-opaque dye injection studies have demonstrated variable leakage from the canal through the sacral foraminae.[8] Furthermore, a relationship between age, height and the level of anaesthesia achieved with caudal extradural block has not been found[9] although this has been reported after lumbar extradural block.[10] Our study did, however, demonstrate some relationship between height and volume of the canal and weight and volume of the canal, although there was no relationship between age and volume.

Previous cadaver work has also shown wide variation in the position of the inferior extremity of the dura with a "mean" position adjacent to the middle third of the body of S2.[2] In our study, the median position was also at the middle third of S2.

We found the mean shortest distance from the dura to the upper limit of the SCM to be longer than previous post-mortem findings, although the ranges were similar (60.5 mm, range 34–80 mm *vs* 47.4 mm, range 19–75mm).[2] The lower dimensions of these ranges are most relevant to clinical practice as the length of the needle performing the caudal block must be chosen carefully so as to avoid puncturing the dura. A 21-gauge, 40-mm "green" needle is often used to perform a caudal block. If this needle were inserted fully into the caudal space, there would be some patients in whom dural puncture might occur. Even a 23-gauge "blue" needle with a length of 25 mm should be used with caution.

In summary, we suggest that to increase the chances of performing a successful caudal block with minimal risk of dural puncture, the needle or cannula should enter the SCM in its upper third at 90° followed by caudal depression through an angle of 55–60° and advancement along the canal no more than is necessary (remembering that the shortest distance to the dural sac ranges from 34 mm in our study and 19 mm in a previous study). An absent hiatus and SCM should be considered if the block proves difficult or impossible to perform.

## Acknowledgement

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*British Journal of Anaesthesia* 1997; 78: 396–399

# I.m. midazolam as premedication produces a concentration-dependent decrease in core temperature in male volunteers

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## Summary

We tested the hypothesis that premedication with i.m. midazolam decreases core temperature dose-dependently. We studied six male volunteers, in random order, on 3 days: (1) no midazolam administration (control day), (2) midazolam 0.025 mg $kg^{-1}$ i.m., (3) midazolam 0.075 mg $kg^{-1}$ i.m. On the first day, subjects were maintained alert during a 30-min control period. On the second and third days, midazolam 0.025 or 0.075 mg $kg^{-1}$ was administered i.m. Core temperatures were measured at the right tympanic membrane. Four adhesive skin surface probes were fixed on the chest, upper right arm, lateral calf and thigh. Finger tip perfusion was evaluated using forearm minus fingertip and calf minus toe, skin surface temperature gradients. Thirty minutes after midazolam i.m., the level of sedation in the volunteers was assessed. Peripheral venous blood was obtained immediately after the assessment of the level of sedation. Tympanic membrane temperatures after administration of midazolam 0.075 mg $kg^{-1}$ i.m. were significantly lower than those on the control and midazolam 0.025 mg $kg^{-1}$ i.m. days at 20 and 30 min. The decreases in tympanic membrane temperatures at 30 min after midazolam i.m. became larger as the volunteers were more deeply sedated. I.m. midazolam produced a concentration-dependent decrease in tympanic membrane temperature at 30 min after midazolam 0.025 and 0.075 mg $kg^{-1}$ i.m. We conclude that midazolam impaired tonic thermoregulatory vasoconstriction, allowing core-to-peripheral heat redistribution in a dose-dependent manner after i.m. administration. (*Br. J. Anaesth.* 1997; **78**: 396–399).

**Key words**
Hypnotics benzodiazepine, midazolam. Premedication, midazolam. Sedation. Temperature, effects. Temperature, monitoring.

Midazolam is a commonly used sedative and anaesthetic adjuvant and the first clinically used water-soluble benzodiazepine. Furthermore, midazolam was the first benzodiazepine that was produced primarily for use in anaesthesia.[1] Its effects on the central nervous system, respiratory system and cardiovascular system have been studied.[2] Although it is widely administered i.m. as premedication, little is known of its effect on thermoregulation. In a preliminary study, we found that premedication with i.m. midazolam decreased core temperature in surgical patients. We speculated that midazolam, in common with other anaesthetic adjuvants, impaired tonic thermoregulatory vasoconstriction, allowing core-to-peripheral heat redistribution.[3 4] Therefore, we tested the hypothesis that midazolam as i.m. premedication decreases core temperature dose-dependently.

## Subjects and methods

With the approval of the Committee on Human Research at the Yamanashi Medical University, we studied six male volunteers. None was obese, receiving medication or had a history of thyroid disease, dysautonomia or Raynaud's syndrome.

Volunteers were studied, in random order, on 3 days: (1) no midazolam administration (control day), (2) midazolam 0.025 mg $kg^{-1}$ i.m., (3) midazolam 0.075 mg $kg^{-1}$ i.m. All studies started at approximately 09:30. Volunteers fasted for 8 h before arriving at the laboratory. They were minimally clothed and covered with a single cotton blanket, and rested supine in a room at a temperature of 22–23 °C during the study.

On the first day subjects were maintained alert during a 30-min control period to avoid the effect of sleep on core and peripheral temperatures.[5] On the second and third days, midazolam 0.025 mg $kg^{-1}$ or 0.075 mg $kg^{-1}$ was administered i.m. Volunteers were kept in a quiet environment for 30-min after midazolam i.m.

Temperatures were monitored using Mon-a-Therm thermocouples (Mallinckrodt Anesthesiology Products, Inc., St Louis, MO, USA). The probes were connected to Mallinckrodt Model 6510

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two-channel electronic thermometers. Core temperature was measured at the right tympanic membrane. The aural probe was inserted until volunteers felt the thermocouple touch the tympanic membrane; appropriate placement was confirmed when they easily detected a gentle rubbing of the attached wire. The probe was then taped securely in place and the aural canal occluded with cotton. Four adhesive skin surface probes were fixed on the chest, upper right arm, lateral calf and thigh. Mean skin temperature (MST) was calculated as $0.3\times(T_{\mathrm{chest}}+T_{\mathrm{arm}})+0.2\times(T_{\mathrm{thigh}}+T_{\mathrm{calf}})$.[6] Mean body temperature (MBT) was calculated as $0.34\times T_{\mathrm{MST}}+0.66\times T_{\mathrm{tym}}$.[7] Finger tip perfusion was evaluated using forearm minus fingertip and calf minus toe, skin surface temperature gradients. Perfusion was recorded from an arm and a leg which did not have an arterial pressure cuff or pulse oximeter.

Thirty minutes after administration of midazolam i.m., the level of sedation was assessed by a blinded observer according to the alertness/sedation scale.[8] The sedation scale is composed of four assessment categories: responsiveness, speech, facial expression and eyes. Each category is assessed. Responsiveness should be evaluated first. The composite score is assigned corresponding to the lowest levels at which any statement is checked. The composite score level ranges from 5 (alert) to 1 (deep sleep).

Peripheral venous blood was obtained immediately after measurement of sedation. Serum concentrations of midazolam were measured as follows: to the 0.25 ml of specimen was added 0.25 ml of sodium carbonate solution 1 mol $\mathrm{litre}^{-1}$, 50 μl of internal standard (prazepam) solution (1 μg $\mathrm{ml}^{-1}$ in $CHCl_3$ : benzene=10 : 9) and 3 ml of extracted solvent ($CHCl_3$ : benzene=10 : 9). The mixture was shaken for 10 min and centrifuged at 3000 rpm for 10 min. The 2 ml of separated organic layer was placed in a glass tube and evaporated to dryness under nitrogen at 35 °C. The residue was redissolved in 30 μl of toluene. A portion of this toluene solution was injected into the gas chromatograph (Hewlett Packard 5880A Series II, CA, USA).

Heart rate and oxyhaemoglobin saturation were measured continuously using pulse oximetry (Symphony N-3000, Nellcor Inc., CA, USA), and arterial pressure was determined oscillometrically at the left arm at the start and end of the study.

### DATA ANALYSIS

Haemodynamic responses, ambient temperature, oxyhaemoglobin saturation, and mean skin and mean body temperatures on each study condition were averaged between volunteers. Results for each study condition were compared using repeated-measures analysis of variance and Scheffé *F* tests. All results are presented as mean (SD) (range). $P<0.05$ was considered statistically significant.

## Results

Mean height of the volunteers was 169 (6) (160–177) cm, body weight 67 (11) (55–85) kg, age 30 (27–36) yr and basal surface area 1.8 (0.2) (1.6–2.1) $\mathrm{m}^2$. Ambient temperatures, mean arterial pressures, heart rates and oxyhaemoglobin saturation were comparable on the 3 study days. Mean skin temperatures on the midazolam 0.075 mg $\mathrm{kg}^{-1}$ day were significantly higher than those on the midazolam 0.025 mg $\mathrm{kg}^{-1}$ day. Mean body temperatures on the midazolam 0.025 and 0.075 mg $\mathrm{kg}^{-1}$ days were significantly lower than those on the control day (table 1).

Tympanic membrane temperatures on the midazolam 0.075 mg $\mathrm{kg}^{-1}$ i.m. day were significantly lower than those on the control and midazolam 0.025 mg $\mathrm{kg}^{-1}$ i.m. days at 20 and 30 min (fig. 1, table 2).

The decreases in tympanic membrane temperatures at 30 min after midazolam i.m. became larger

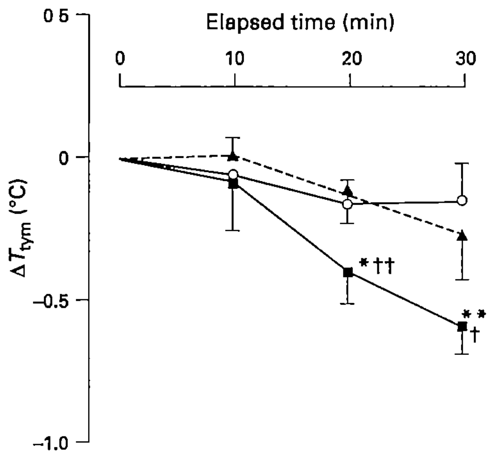

*Figure 1* Changes in tympanic membrane temperature ($\Delta T_{\mathrm{tym}}$) at 10, 20 and 30 min after administration of midazolam i.m. Tympanic membrane temperatures on the midazolam 0.075 mg $\mathrm{kg}^{-1}$ i.m. day (■) were significantly lower than those on the control (○) and midazolam 0.025 mg $\mathrm{kg}^{-1}$ i m. (▲) days at 20 and 30 min. Time zero=just before midazolam i.m. Values are mean (SD). $^*P<0.05$, $^{**}P<0.01$ compared with control day; $^\dagger P<0.05$, $^{\dagger\dagger}P<0.01$ compared with value on the midazolam 0.025 mg $\mathrm{kg}^{-1}$ i.m. day.

*Table 1* Study conditions at each midazolam concentration (mean (SD) [range]). $^{**}P<0.01$ *vs.* control; $^{\dagger\dagger}P<0.01$ *vs* 0.025 mg $\mathrm{kg}^{-1}$

| | Control | Midazolan 0.025 mg $\mathrm{kg}^{-1}$ | Midazolan 0.075 mg $\mathrm{kg}^{-1}$ |
|---|---|---|---|
| Ambient temperature (°C) | 21.8 (0.7) [20.6–22.6] | 22.1 (0.8) [20.8–23.5] | 22.2 (0.5) [21.7–22.7] |
| Mean arterial pressure (mm Hg) | 81 (6) [67–89] | 80 (5) [74–90] | 81 (7) [72–98] |
| Heart rate (beat $\mathrm{min}^{-1}$) | 67 (14) [48–94] | 65 (13) [47–87] | 66 (13) [46–82] |
| Oxyhaemoglobin saturation (%) | 98 (2) [97–100] | 98 (1) [96–100] | 97 (2) [95–100] |
| Mean skin temperature (°C) | 33.7 (0.5) [32.8–34.8] | 33.4 (0.4) [33.1–34.6] | 33.9 (0.4) [33.0–34 3]†† |
| Mean body temperature (°C) | 35.9 (0.2) [35.6–36.3] | 35.7 (0.3) [35.3–36.2]** | 35.7 (0.3) [35.1–36.2]** |

*Table 2* Change in temperatures 30 min after the start of the study (mean (SD) [range]). $^{**}P<0.01$ *vs* control. $^{\dagger}P<0.05$ *vs* 0.025 mg kg$^{-1}$

| | Control | 0.025 mg kg$^{-1}$ | 0.075 mg kg$^{-1}$ |
|---|---|---|---|
| ΔTympanic membrane temperature (°C) | −0.1 (0.1)<br>[−0.3 to 0] | −0.3 (0.2)<br>[−0.5 to −0.1] | −0.6 (0.1)**†<br>[−0.8 to −0.5] |
| ΔGradient (arm–finger) (°C) | 1.5 (1.8)<br>[−0.1 to −4.9] | −3.7 (2.4)**<br>[−7.3 to −1.5] | −5.6 (3.9)**<br>[−11.7 to −0.8] |
| ΔGradient (calf–toe) (°C) | 0.9 (1.4)<br>[−0.5 to −2.7] | −1.5 (3.1)**<br>[−7.6 to −1.0] | −7.4 (4.1)**<br>[−11.1 to −0.5] |

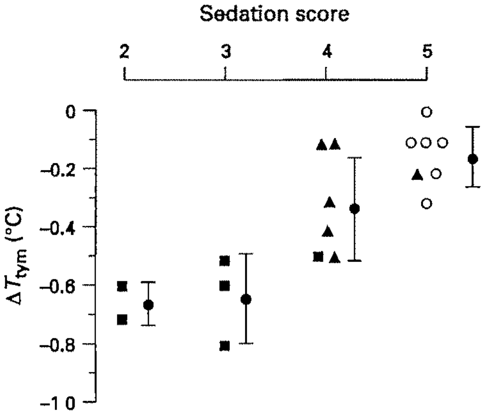

*Figure 2* Changes in tympanic membrane temperature ($\Delta T_{tym}$) at 30 min after midazolam i.m. *vs* the observer's assessment of alertness/sedation scale. ○= Control day; ▲=midazolam 0.025 mg kg$^{-1}$ i.m. day; ■=midazolam 0.075 mg kg$^{-1}$ i.m. day.

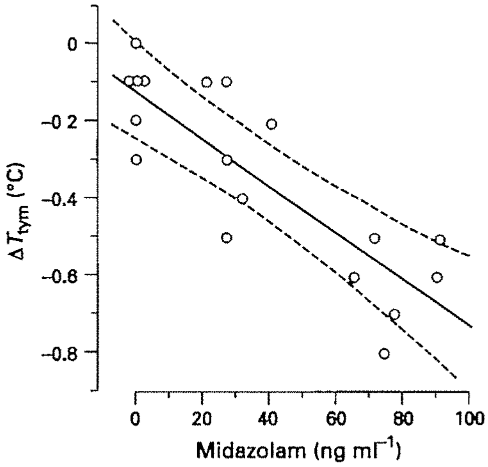

*Figure 3* Midazolam produced a concentration-dependent decrease in tympanic membrane temperature 30 min after i.m. administration. —=Regression line, with dashed lines showing 95% confidence limits: $T_{tym}$ (°C)=−0.006 (midazolam (°C ng$^{-1}$ ml$^{-1}$))−0.124, $r^2$=0.698.

as the volunteers were more deeply sedated (fig. 2).

Figure 3 shows the regression for changes in tympanic membrane temperatures against blood concentrations of midazolam at 30 min after midazolam i.m. Midazolam linearly decreased core temperature.

The changes in skin surface temperature using forearm minus fingertip gradients (Δgradient (arm−finger)) and calf minus toe gradients (Δgradient (calf−toe)) at 30 min after midazolam i.m. on the midazolam 0.025 and 0.075 mg kg$^{-1}$ i.m. days were significantly larger than those on the control day (table 2).

## Discussion

Benzodiazepines have established themselves as useful drugs for premedication because of their sedative and anxiolytic effects, and good tolerance.[9] Midazolam is a benzodiazepine derivative with very rapid absorption, which is almost complete within 1 h, and peak concentrations are achieved in 30 min after i.m. administration.[10 11] Midazolam i.m. has been shown to be effective when used for preoperative sedation.[12] In this study, i.m. midazolam produced a concentration-dependent decrease in tympanic membrane temperature. This study was a simulation to test the effect of premedication with midazolam on core and peripheral temperatures in young volunteers.

Core temperature usually decreases by 0.5–1.5 °C during the first hour after induction of general anaesthesia.[13] In previous studies, even induction of general anaesthesia slightly increased cutaneous heat loss[14] and decreased metabolic heat production by 33%.[15] It is thus impossible to explain core hypothermia during the first hour of anaesthesia by this imbalance (metabolic heat production minus cutaneous heat loss). The decrease in heat production after administration of midazolam is less than that after induction of anaesthesia.[16] Accordingly, the imbalance between heat production and cutaneous heat loss contributed little to core hypothermia after i.m. administration of midazolam.

One possible mechanism for the decrease in core temperature is altered distribution of heat within the body. Heat is usually not distributed evenly within the body because tonic thermoregulatory vasoconstriction typically maintains a significant core-to-peripheral temperature gradient.[3 17] In this study, the Δgradients (arm−finger) and (calf−toe) showed a significant reduction (table 2) and indicated that core-to-peripheral heat redistribution occurred inside the body after administration of midazolam i.m. As the specific heat of most tissue is similar, heat content is greater in core than peripheral tissues. Although i.m. midazolam only slightly increases cutaneous heat loss, midazolam-induced vasodilatation allows redistribution of heat from the core thermal compartment to peripheral tissues. This process markedly decreases core temperature.

I.m. midazolam caused a linear decrease in core temperature in this study, proportional to its blood concentration. Clinically, for sedation as preoperative premedication, midazolam 0.07–0.10 mg kg$^{-1}$ i.m. is the dose range that has been studied and recommended.[2 12] We had observed in our preliminary study that all patients exhibited vasoconstriction before receiving midazolam i.m. as premedication. Therefore, the doses of midazolam usually used for premedication should decrease core temperature significantly. As midazolam and its active metabolite, α-hydroxy-midazolam, are eliminated with half-lives of approximately 3 h, our results are applicable to real clinical situations.[18]

## Acknowledgements

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*British Journal of Anaesthesia* 1997; 78: 400–406

# Effect of clonidine and dexmedetomidine premedication on perioperative oxygen consumption and haemodynamic state

M. T. TAITTONEN, O. A. KIRVELÄ, R. AANTAA AND J. H. KANTO

## Summary

Premedication has been shown to affect both oxygen consumption and metabolic rate. We have compared the perioperative metabolic and haemodynamic effects of two $\alpha_2$-agonists, clonidine and the more selective dexmedetomidine, in 30 ASA I patients undergoing plastic surgical procedures under general anaesthesia. Patients were premedicated with clonidine 4 $\mu g\ kg^{-1}$ ($n=10$), dexmedetomidine 2.5 $\mu g\ kg^{-1}$ ($n=10$) or saline ($n=10$) i.m. The doses of clonidine and dexmedetomidine were intended to be equipotent. The maximum decrease in preoperative oxygen consumption was 8% and decreases in systolic and diastolic arterial pressures were 11% from baseline after clonidine and dexmedetomidine. During operation, the maximum reduction in heart rate was 18% in the clonidine and dexmedetomidine groups compared with the placebo group. After operation, the maximum decrease in systolic arterial pressure was 11%, diastolic arterial pressure 15% and oxygen consumption 17% in the clonidine and dexmedetomidine groups compared with placebo. In summary, both clonidine 4 $\mu g\ kg^{-1}$ and dexmedetomidine 2.5 $\mu g\ kg^{-1}$ decreased perioperative oxygen consumption effectively, with a similar haemodynamic profile. (*Br. J. Anaesth.* 1997; **78**: 400–406).

**Key words**
Sympathetic nervous system, clonidine. Sympathetic nervous system, dexmedetomidine. Cardiovascular system, effects. Oxygen, consumption.

$\alpha_2$-Agonists are currently used as sedatives and anaesthetics in veterinary anaesthesia and clonidine is also used as an adjunct to anaesthesia and as an extradural–intrathecal analgesic in humans.[1] Both clonidine and dexmedetomidine, a more selective and specific $\alpha_2$-agonist, have been shown to decrease induction doses of i.v. anaesthetics and to decrease intraoperative opioid and volatile anaesthetic requirements for maintenance of anaesthesia.[1] In addition, they have been shown to decrease perioperative catecholamine concentrations[1 2] and promote perioperative haemodynamic and adrenergic stability.[1]

Perioperative stress associated with surgery and anaesthesia evokes an endocrine response that includes stimulation of the sympathetic nervous system.[3] This increases circulating plasma adrenaline and noradrenaline concentrations with consequent increases in arterial pressure, heart rate and oxygen consumption.[3 4] Controlling this perioperative stress response is an important goal of modern anaesthesia.[5]

We have compared the perioperative metabolic and haemodynamic effects of clonidine and dexmedetomidine to determine if the more selective agonist, dexmedetomidine, has any clinical advantages over clonidine.

## Patients and methods

The study was double-blind, randomized and placebo-controlled, and was approved by the Ethics Committee of Turku University Hospital. After obtaining written informed consent, we studied 30 ASA I patients undergoing elective plastic surgical procedures under general anaesthesia (table 1). Patients with known drug hypersensitivity were excluded.

Patients entered the hospital 1 day before the scheduled surgery and were interviewed and examined. Routine laboratory testing was performed. No hypnotic medication was given on the evening before surgery.

After fasting overnight, patients were transferred to the recovery room where pre- and postoperative assessments were performed. Patients were resting supine in their hospital beds and were allowed to listen to music of their choice. Measurements were started at 08:00–09:00.

On arrival in the study area, ungraded visual analogue scales (VAS) were introduced and preoperative baseline anxiety, tiredness and dryness of the mouth were assessed. If the patient was asleep during the later course of the session and could not be awakened by voice command a score of zero was recorded for anxiety and a score of 100 was recorded for tiredness. In such case dryness of mouth was not recorded.

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Before the metabolic measurements, continuous monitoring of the electrocardiogram and heart rate (HR), together with non-invasive recording of systolic (SAP), mean (MAP) and diastolic (DAP) arterial pressures (Cardiocap II, Datex/Instrumentarium, Helsinki, Finland) was commenced. Arterial haemoglobin oxygen saturation ($Sp_{O_2}$) was measured using pulse oximetry (Cardiocap II, Datex/Instrumentarium, Helsinki, Finland). The recordings were made at 5-min intervals (before, during and after operation).

After assessment of baseline tiredness, anxiety and dryness of mouth and a 15-min stabilization period under the metabolic monitor canopy (see below), metabolic measurements, energy expenditure (EE), oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were started. The first consecutive 15 min after stabilization were used for determining baseline metabolic and haemodynamic values. After these baseline measurements patients were premedicated.

Patients were allocated randomly to receive clonidine 4 $\mu$g kg$^{-1}$ (Catapresan, Boehringer Ingelheim, Ingelheim am Rhein, Germany), dexmedetomidine 2.5 $\mu$g kg$^{-1}$ (provided by Orion Corporation, Orion-Farmos, Turku, Finland) or placebo (3 ml of 0.9% NaCl) in a double-blind manner. Drugs were administered into the deltoid muscle 40–50 min before anticipated induction of anaesthesia. The doses of clonidine and dexmedetomidine were selected to provide comparable preoperative effects.[6 7]

The double-blind nature of the study was ensured by having an independent nurse, not participating in the study, prepare clonidine or dexmedetomidine in ready-to-inject forms by dilution in 3 ml with physiological saline.

After premedication, metabolic and haemodynamic values were recorded for 30 min. Metabolic measurements (before and after operation) were made at 1-min intervals and the recorded values were means of 15 consecutive measurements. VAS scores for tiredness, anxiety and dryness of mouth were recorded 30 min after premedication, that is at the end of the preoperative study session. Patients were then transferred to the operating room and anaesthesia was induced 10–20 min after completion of the preoperative follow-up period.

During operation, SAP, MAP, DAP, $Sp_{O_2}$ and HR were recorded for 45 min. The first value was recorded 5 min before induction of anaesthesia and the second value 5 min after tracheal intubation. Recording of EE, $\dot{V}O_2$ and $\dot{V}CO_2$ was started 15–30 min after intubation, when equilibrium of end-tidal carbon dioxide (4.5–5%) had been achieved with controlled ventilation. The ventilator settings (tidal volume, breath rate, $FI_{O_2}$) were not altered thereafter. Metabolic measurements were performed during surgery at 1-min intervals and the recorded values were means of five consecutive measurements. Metabolic values were recorded for 30 min because of differences in duration of anaesthesia and surgery and thus incomplete data thereafter.

After operation SAP, MAP, DAP, HR, $Sp_{O_2}$, EE, $\dot{V}O_2$ and $\dot{V}CO_2$ values were recorded for 90 min. Metabolic monitoring was started as soon as the patient required no ventilatory assistance or supplementary oxygen to comply with $Sp_{O_2}$ >90% after tracheal extubation. VAS scores for tiredness, anxiety and dryness of mouth were recorded at the end of the 90 min postoperative measurement period. Postoperative shivering (yes/no) and analgetic requirements were recorded.

### METABOLIC MEASUREMENTS

Metabolic measurements were performed using a portable metabolic cart system (Deltatrac, Datex/Instrumentarium, Helsinki, Finland). The Deltatrac is an open system, indirect calorimetry device designed to measure $\dot{V}O_2$ and $\dot{V}CO_2$ in both spontaneously breathing patients and those undergoing mechanical ventilation.[8] Deltatrac has been shown to have good overall accuracy (in a respirator model: mean error 2±2 % for $\dot{V}CO_2$ and 4±4 % for $\dot{V}O_2$[8]; in a canopy model: mean error 3±2 % for $\dot{V}CO_2$ and 4±2 % for $\dot{V}O_2$[8]). Flow calibration was performed by alcohol burning before the study. The monitor was calibrated further using a standard gas mixture containing 95% oxygen and 5% carbon dioxide, before each session.

For measurements in spontaneously breathing patients the subject's head was placed under a plastic cone (canopy) connected to the analyser. The canopy was half-ellipsoidal and made of 1-mm thick transparent PVC plastic. It has adapters for tubing and with a wide edge of soft plastic cloth to make construction airtight around the head and neck of the subject. Minor leakages do not affect the results as they are directed inwards because of the slight underpressure inside the canopy caused by the constant airflow (40 litre min$^{-1}$) drawn through the canopy to the gas analysers, and thus all expired gases are captured. The difference between inspired (sampling at the entry valve of the canopy) and expired oxygen fractions ($FI_{O_2}$, $FE'_{O_2}$) is measured with a fast-response paramagnetic differential oxygen sensor (OM-101, Datex/Instrumentarium, Helsinki, Finland). The expired carbon dioxide fraction ($FE'_{CO_2}$) is measured with an infrared carbon dioxide sensor. A microcomputer controls a set of magnetic valves for automatic control of absolute $FI_{O_2}$, the inspired carbon dioxide fraction ($FI_{CO_2}$) and gas analyser baselines. During mechanical ventilation the device is connected to the outlet port of the ventilator and expired air is collected through a built-in mixing chamber. The mixed expiratory gases are then diluted in the mainstream of the constant flow generator. $FI_{O_2}$ and $FI_{CO_2}$ are measured from the inspiratory limb of the ventilator, and $FE'_{O_2}$ and $FE'_{CO_2}$ from the mixing chamber. The fraction of carbon dioxide in the diluted expiratory gases, downstream from the flow generator, is also measured.

$\dot{V}CO_2$ was calculated in both canopy and ventilator measurements as the product of constant flow and fraction of carbon dioxide in diluted expiratory flow: $\dot{V}CO_2 = Q \times FE'_{CO_2}$, where $Q$=constant flow.

With the canopy, $\dot{V}O_2$ is calculated using the Haldane transformation[9]:

$$\dot{V}O_2=(Q/(1-F\mathrm{I}_{O_2}))\times(F\mathrm{I}_{O_2}-F\mathrm{E}'_{O_2}-F\mathrm{I}_{O_2}\times(F\mathrm{E}'_{CO_2}-F\mathrm{I}_{CO_2}))$$

where $F\mathrm{E}'_{O_2}$ and $F\mathrm{E}'_{CO_2}$=fractions of oxygen and carbon dioxide in mixed expiratory gas flowing through the monitor.

During ventilator measurement, RQ was calculated using the Haldane transformation from the gas fractions[9]: $RQ=1-F\mathrm{I}_{O_2}/(F\mathrm{I}_{O_2}-F\mathrm{E}'_{O_2})/F\mathrm{E}'_{CO_2}-F\mathrm{I}_{O_2}$, where $F\mathrm{E}'_{O_2}$ and $F\mathrm{E}'_{CO_2}$ were measured from the mixing chamber. The expiratory gases from the respirator flow through the mixing chamber and then form a constant flow and concentration through the system. $\dot{V}CO_2$ was calculated as the product of constant flow and concentration of carbon dioxide downstream from the mixing chamber identical to the canopy measurement. $\dot{V}O_2$ was subsequently calculated from RQ as: $\dot{V}O_2=\dot{V}CO_2/RQ$.

Energy expenditure (EE) was calculated from the measured rates of $\dot{V}O_2$ and $\dot{V}CO_2$: $EE=3.581\times\dot{V}O_2+1.448\times\dot{V}CO_2-32.4$, where EE is given in kcal day$^{-1}$, $\dot{V}O_2$ in litre day$^{-1}$, and $\dot{V}CO_2$ in litre day$^{-1}$.[8 10]

All calculations were performed at 1-min intervals, and the results were stored for further processing.

### ANAESTHETIC MANAGEMENT

On arrival in the operating theatre, peripheral i.v. infusion of lactated Ringer's solution was started. No glucose was infused during the study. Immediately before induction of anaesthesia, patients received fentanyl (Fentanyl, Orion Corporation, Medipolar, Oulu, Finland) 2 μg kg$^{-1}$ i.v. While patients breathed 100% oxygen via a face mask, anaesthesia was induced with propofol 2–2.5 mg kg$^{-1}$. Atracurium 0.5 mg kg$^{-1}$ was given i.v. to facilitate laryngoscopy and tracheal intubation. For further neuromuscular block, atracurium was administered to maintain 95% block, as assessed by a neurostimulator (Innervator NS 252, Fisher and Paykel Electronics Ltd, Healthcare Division, Auckland, NZ). Anaesthesia was maintained with infusion of propofol 6–8 mg kg$^{-1}$ h$^{-1}$. Patients also received fentanyl bolus doses of 1 μg kg$^{-1}$ at 30-min intervals. Signs of inadequate anaesthesia (i.e. HR or SAP >20% of pre-induction values, lacrimation, sweating and flushing) were treated by increasing the rate of infusion of propofol and by administering an i.v. bolus of fentanyl 1 μg kg$^{-1}$. Controlled ventilation (Servo 900D, Siemens-Elema, Solana, Sweden) with 30% oxygen in air was adjusted before the metabolic measurements to maintain an end-tidal carbon dioxide concentration (Cardiocap II, Datex/Instrumentarium, Helsinki, Finland) of 4.5–5%. End-tidal carbon dioxide was not measured during metabolic measurements to avoid leaks from the closed gas system. Inspiratory oxygen was stabilized using an extra humidifier in the ventilator inspiratory limb. Oesophageal temperature measurement was started immediately after tracheal intubation. Temperature of the patient was kept at more than 36 °C by warming the fluids and operating tables and by using warmed cotton blankets placed over the patient during and after operation.

Hypotension was treated primarily by decreasing the infusion rate of propofol. Bradycardia, defined as HR <40 beat min$^{-1}$, was treated with a bolus dose of atropine 1 mg i.v. At the end of surgery patients were allowed to recover spontaneously from neuromuscular block. The trachea was extubated when sufficient spontaneous ventilation was evident.

### STATISTICAL ANALYSIS

For repetitive data (SAP, MAP, DAP, HR, $Sp_{O_2}$, $\dot{V}O_2$, $\dot{V}CO_2$), differences between groups were analysed using two-way repeated measures analysis of covariance (ANCOVA), with time as the within-factor and drug as the between-factor. When a statistically significant drug effect or drug×time interaction was present, the analysis was continued by applying contrasts for each group.[11] The comparability of the groups with respect to patient and operational characteristics was analysed using one-way analysis of variance (ANOVA) or chi-square test (sex, number of patients requiring supplementary oxygen). VAS scores were analysed using ANOVA.[12] $P<0.05$ was considered significant.

## Results

The groups were similar in patient and operational characteristics (table 1). None of the patients needed blood products or colloids.

Dryness of mouth and tiredness increased towards the end of the preoperative follow-up period

*Table 1* Patient and operational characteristics (mean (SD or range) or number). BMR=Baseline metabolic rate, measured by indirect calorimetry; Anaesthesia=duration of anaesthesia; Surgery=duration of surgery. Propofol, fentanyl and atracurium doses are total doses. No significant differences in patient or operational characteristics between groups

| Variable | Dexmedetomidine group | Clonidine group | Placebo group |
|---|---|---|---|
| Age (yr) | 42.4 (27–56) | 35.8 (19–61) | 39.4 (22–53) |
| Sex (M/F) | 3/7 | 3/7 | 2/8 |
| Height (cm) | 166.7 (11.5) | 166.9 (5.7) | 167.7 (11.2) |
| Weight (kg) | 72.5 (13.8) | 67.4 (13.8) | 71.8 (21.7) |
| BSA (m$^2$) | 1.8 (0.2) | 1.7 (0.3) | 1.8 (0.3) |
| BMR (kcal/24 h) | 1554.0 (265.3) | 1670.2 (392.9) | 1570.1 (327.5) |
| Anaesthesia (min) | 117.5 (58.6) | 99.5 (39.6) | 106.5 (58.5) |
| Surgery (min) | 76.5 (53.5) | 60 (32.5) | 60 (56) |
| Atracurium (mg) | 61.5 (24.4) | 74.9 (28.8) | 68.3 (24.0) |
| Fentanyl (μg) | 405 (140.8) | 372.5 (137.7) | 367.5 (63.5) |
| Propofol (mg) | 880.0 (422.2) | 749.0 (399.6) | 771 4 (359.2) |

*Table 2* VAS-scores for tiredness, anxiolysis and dryness of mouth (mean (SD)). I=Baseline; II=30 min after study drug; III=at the end of the 90 min postoperative follow-up period. *Significant difference in dryness of mouth between dexmedetomidine and placebo groups ($P$=0.018)

| | Dexmedetomidine group | Clonidine group | Placebo group |
|---|---|---|---|
| Anxiolysis I | 30.2 (24.7) | 36.1 (33.7) | 33.6 (35.1) |
| Anxiolysis II | 23.0 (17.1) | 27.4 (26.8) | 17.5 (21.9) |
| Anxiolysis III | 6.1 (9.3) | 20.4 (23 7) | 8.2 (15.7) |
| Dryness of mouth I | 21.1 (23.4) | 13.8 (15 9) | 15 7 (22 0) |
| Dryness of mouth II | 48.7 (32 0)* | 29.0 (30.4) | 13.8 (16 9) |
| Dryness of mouth III | 50.7 (31.2) | 50.2 (31.4) | 43.3 (35 3) |
| Tiredness I | 23.6 (23.7) | 22.2 (16.8) | 10.8 (14 2) |
| Tiredness II | 52.0 (23.4) | 60 1 (21.3) | 28.8 (25 4) |
| Tiredness III | 55.7 (24.9) | 52.8 (39.4) | 37.0 (25.7) |

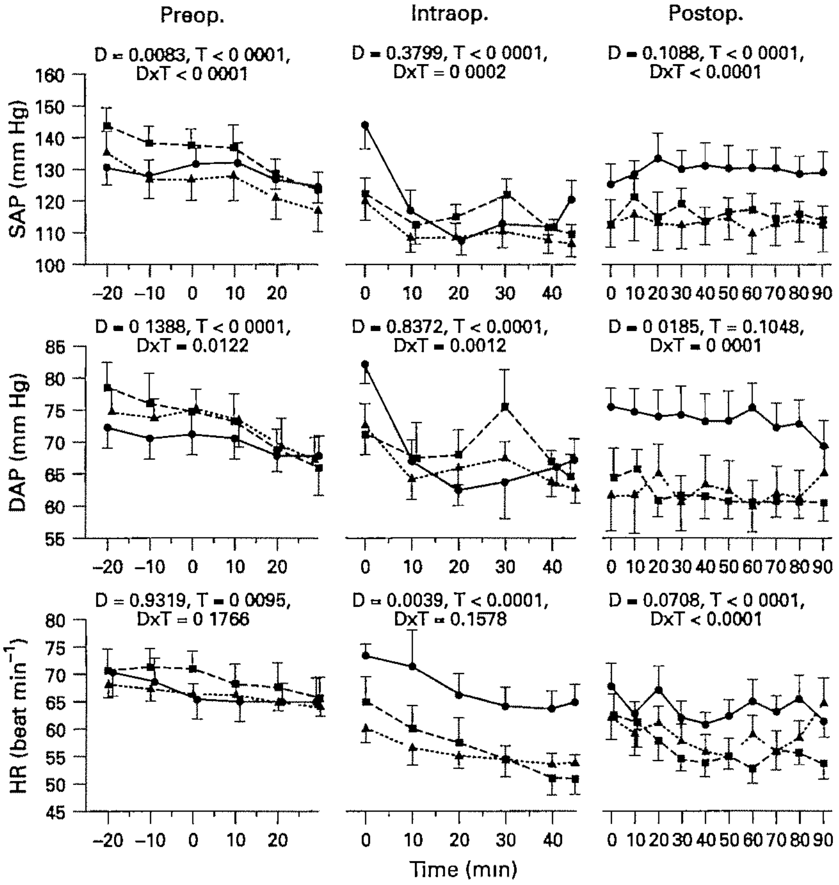

*Figure 1* Perioperative heart rate (HR), systolic (SAP) and diastolic (DAP) arterial pressure (mean, SD) in the placebo (●), clonidine (■) and dexmedetomidine (▲) groups. Before operation (Preop.) drug administration was at time 0; during operation (Intraop.) time 0=5 min before induction of anaesthesia and time 10=10 min after tracheal intubation. D=$P$ value for drug effect; T=$P$ value for time effect; DxT=$P$ value for drug×time interaction in overall ANCOVA.

($P$≤0.001 for time factor) in all three groups, with dexmedetomidine causing more dryness of mouth than placebo ($P$=0.018 in pairwise comparisons) (table 2). There were no significant differences in tiredness between groups (table 2).

Before operation, SAP and MAP decreased after clonidine ($P$=0.0044 and $P$=0.0090, respectively, in pairwise comparisons) and dexmedetomidine ($P$=0.014 and $P$=0.016, respectively, in pairwise comparisons) compared with placebo. Clonidine also decreased DAP compared with placebo ($P$=0.048 in pairwise comparisons). The mean maximum decrease in SAP and DAP after clonidine was 11% from baseline values (fig. 1).

Pre-induction values of SAP, MAP and DAP, measured 5 min before induction of anaesthesia, were lower in the clonidine and dexmedetomidine groups ($P$<0.05 in pairwise comparisons) and HR was lower in the dexmedetomidine group than in the placebo group ($P$=0.025 in pairwise comparisons). One female patient with a HR of 38 beat min$^{-1}$ before laryngoscopy in the dexmedetomidine group had a sinus pause during intubation. The sinus pause lasted for approximately 3 s and was treated with atropine 1 mg i.v. This patient was excluded from the study. No other patient needed atropine or any other vasoactive agent during the study.

During operation, HR was lower (approximately 18%) in the clonidine and dexmedetomidine groups compared with the placebo group ($P$=0.0047 and

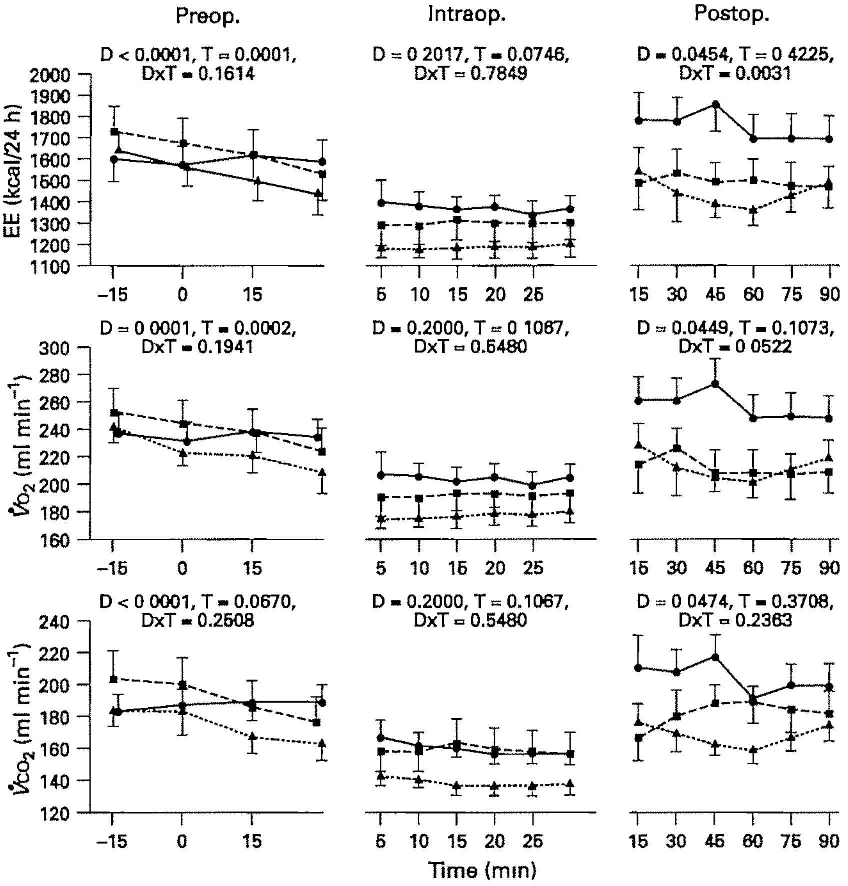

*Figure 2* Perioperative oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$) and energy expenditure (EE) (mean, SD) in the placebo (●), clonidine (■) and dexmedetomidine (▲) groups. Before operation (Preop.) drug administration was at time 0. During intraoperative (Intraop.) metabolic measurements, surgery was proceeding. D=*P* value for drug effect; T=*P* value for time effect; DxT=*P* value for drug×time interaction in overall ANCOVA.

$P$=0.0032, respectively, in pairwise comparisons) (fig. 1).

After operation, SAP was lower in the dexmedetomidine group ($P$=0.045 in pairwise comparisons) and HR was lower in the clonidine group compared with the placebo group ($P$=0.024 in pairwise comparisons). DAP and MAP were lower after both clonidine ($P$=0.010 and $P$=0.014, respectively, in pairwise comparisons) and dexmedetomidine ($P$=0.0213 and $P$=0.024, respectively, in pairwise comparisons) compared with placebo. SAP was approximately 11% lower and DAP approximately 15% lower in the clonidine and dexmedetomidine groups than in the placebo group (fig. 1).

There were no significant differences in pre- and intraoperative $Sp_{O_2}$ values. After operation, after complete recovery from neuromuscular block, eight patients in the dexmedetomidine group, five in the clonidine and four in the placebo group had clinically inadequate ventilation and required supplementary oxygen during the emergence period immediately after tracheal extubation. There were no differences in the numbers of patients requiring supplementary oxygen ($P$=0.155) or duration ($P$=0.644) of administration of supplementary oxygen between groups.

Before operation, clonidine and dexmedetomidine caused a greater decrease in $\dot{V}O_2$, $\dot{V}CO_2$ and EE than placebo ($P$<0.001 for all variables in pairwise comparisons). There were no differences in RQ between the groups. The maximum decrease in $\dot{V}O_2$, $\dot{V}CO_2$ and EE was 8% from baseline in the clonidine group and 7% from baseline in the dexmedetomidine group (fig. 2).

During operation, there were no differences in the metabolic variables between groups, although $\dot{V}O_2$ and EE tended to be lower in the clonidine and dexmedetomidine groups than in the placebo group (fig. 2).

After operation, $\dot{V}O_2$ was lower (approximately 17%) in the clonidine and dexmedetomidine groups than in the placebo group ($P$=0.049 and $P$=0.021, respectively, in pairwise comparisons) (fig. 2). $\dot{V}CO_2$ and EE were lower after dexmedetomidine (approximately 17% and 19%, respectively) compared with placebo ($P$=0.014 for both variables in pairwise comparisons) (fig. 2).

Patients in the clonidine and dexmedetomidine groups tended to be more sedated than patients in the placebo group, although there were no significant differences between the groups in tiredness after operation ($P$=0.269) (table 2). There were no differences between the groups in postoperative analgesic requirements. One patient in the dexmedetomidine group received metoclopramide for nausea and vomiting. Two patients in the placebo group and none in the clonidine or dexmedetomidine groups experienced shivering after operation.

## Discussion

The $\alpha_2$-agonists, including clonidine and dexmedetomidine, decrease central sympathetic outflow and modify intraoperative cardiovascular and endocrine responses favourably to surgical stimuli and laryngoscopy.[1 2] The reduction in tachycardia, hypertension, sympathetic activity and consequently total body oxygen consumption may be of benefit in patients at risk of developing inadequate cardiac output or myocardial ischaemia.[4 5 13]

In this study both clonidine 4 μg $kg^{-1}$ and dexmedetomidine 2.5 μg $kg^{-1}$ had metabolic effects of similar magnitude. Before operation, the maximum decrease in $\dot{V}O_2$ and EE was 7–8 %. The *t*max value of i.m. clonidine is 54 min[14] and that of dexmedetomidine 1.6 h.[15] Thus a greater decrease may occur during a longer observation period as we recorded $\dot{V}O_2$ and EE for only 30 min. I.v. dexmedetomidine 1–2 μg $kg^{-1}$ has been shown previously to decrease $\dot{V}O_2$ in healthy volunteers.[16] In that study $\dot{V}O_2$ showed a biphasic response, as there was an initial increase in $\dot{V}O_2$, 10 min after drug administration, followed by a sharp decrease below the baseline value, 60 min after drug administration (maximum of 17% on average from baseline). In our study we did not notice an increase in $\dot{V}O_2$. This may be because of slower absorption after i.m. administration and lack of high peak concentrations and consequent haemodynamic effects after an i.v. bolus of clonidine and dexmedetomidine.[1] During operation, $\dot{V}O_2$ and EE tended to be lower in the clonidine and dexmedetomidine groups (fig. 2). However, these differences were not statistically significant because $\dot{V}O_2$ and EE were well controlled by the anaesthetics in all groups. After operation, the decrease in $\dot{V}O_2$ (approximately 17%) observed in this study after clonidine and dexmedetomidine was of similar magnitude to that reported previously after an i.v. bolus of clonidine 2 mg $kg^{-1}$.[17]

Both clonidine and dexmedetomidine have been shown to reduce sympathetic nervous system activity and plasma catecholamine concentrations.[1 2] This results in decreased whole body metabolism while the decrease in cardiac output related to clonidine and dexmedetomidine[13 18] may lead to decreased myocardial oxygen consumption.[18] These combined effects may contribute to the reduction observed in $\dot{V}O_2$ and EE after clonidine and dexmedetomidine. Similarly, the analgesic effects of clonidine and dexmedetomidine[1 14] and the indirect effects of sedation and neuromuscular block[1] might account in part for the reduction in $\dot{V}O_2$. It has been demonstrated that effective analgesia in the postoperative period can decrease $\dot{V}O_2$ by up to 7–8 %.[19]

Recovery from general anaesthesia is associated with shivering and an increase in $\dot{V}O_2$.[20] In our study only two patients in the placebo group had moderate shivering. Although clonidine has been shown to reduce post-anaesthetic shivering,[17] the low incidence of shivering in our study could be explained partly by the anaesthetic conditions: both propofol[21] and fentanyl[22] have been shown to reduce shivering. Patients were also warmed during and after operation to avoid hypothermia.

The metabolic measurements were performed using an open circuit indirect calorimeter. When used in patients undergoing mechanical ventilation these calorimeters are very sensitive to fluctuations in $FI_{O_2}$ and generally invalid with $FI_{O_2}$ values greater than 0.8. This is because of their reliance on the Haldane transformation (HT) to determine $\dot{V}O_2$, which includes an assumption that no other gases apart from oxygen, carbon dioxide and nitrogen are present in the system. Other gases, such as volatile anaesthetics and nitrous oxide, invalidate the equation.[23] To avoid the confounding effects of these gases on HT, we induced and maintained anaesthesia with i.v. propofol and fentanyl and ventilated the lungs of patients with 30% oxygen in air. As open circuit calorimeters are also affected by leaks, analysis of end-tidal carbon dioxide was arrested during the measurement periods. Canopy measurements are not affected by minor leakages as they are directed inward because of the slight underpressure inside the canopy.

The decrease in arterial pressure (AP) and HR after both clonidine and dexmedetomidine premedication was of a similar magnitude (fig. 1). These hypotensive and bradycardic effects of $\alpha_2$-agonists are presumably mediated by activation of $\alpha_2$-adrenoceptors or imidazoline-preferring receptors, or both, in the ventrolateral medulla, especially in the nucleus tractus solitarius.[1 24] In our study AP and HR tended to increase in the dexmedetomidine group but not in the clonidine group at the end of the postoperative follow-up period (fig. 1). This is in line with the pharmacokinetic variables of these compounds. The terminal half-life of a single i.m. bolus of dexmedetomidine is approximately 4 h[7]; that of an i.v. bolus of clonidine is approximately 8.5 h.[25] Hypotension and bradycardia are also major adverse effects of $\alpha_2$-agonists. In our study, one female patient in the dexmedetomidine group had a sinus pause of short duration during intubation with a HR of 38 beat $min^{-1}$ before laryngoscopy. This raises concern regarding the use of $\alpha_2$-agonists in patients with high parasympathetic tone.[1]

$\alpha_2$-Agonists reduce perioperative anaesthetic and analgesic requirements.[1] However, there were no significant differences in opioid or i.v. anaesthetic requirements between the groups in our study, probably because the induction and maintenance doses of fentanyl and propofol were intended to be equipotent in all three groups. This was to avoid the effect of different doses of propofol and fentanyl on postoperative energy metabolism and haemodynamic state.

Although previously reported to be anxiolytic,[1] neither clonidine nor dexmedetomidine provided anxiolysis in our investigation. Baseline anxiety values observed in this study were only moderate in all three groups (table 2). Moreover, most of the surgical procedures were minor and patients showed little apprehension in the ward, making demonstration of anxiolysis difficult.

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# Regional cerebral blood flow (SPECT) during anaesthesia with isoflurane and nitrous oxide in humans

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## Summary

Nitrous oxide and isoflurane have different effects on absolute cerebral blood flow (CBF) and regional distribution of CBF in humans. In this study we examined the effects of isoflurane in combination with nitrous oxide on CBF. We studied 10 patients (two groups of five patients, ASA I) anaesthetized with 50% nitrous oxide and either 0.5 or 1.0 MAC of isoflurane during normocapnia ($Pa_{CO_2}$ 5.7 kPa) using two-dimensional CBF measurement ($CBF_{xenon}$) (i.v. $^{133}$xenon washout technique) and a three-dimensional method for measurement of regional CBF (rCBF) distribution with SPECT (single photon emission computer-aided tomografy with $^{99m}$Tc-HMPAO). The results were compared with 1.0 MAC of isoflurane from a previous study performed in exactly the same way as the present investigation. During normocapnia, anaesthesia with 50% nitrous oxide and 0.5 MAC of isoflurane resulted in a mean $CBF_{xenon}$ of 45 (SEM 5) ISI units. Increasing the isoflurane concentration to 1.0 MAC had no significant effect on mean $CBF_{xenon}$ (53 (5) ISI units). Both flow values were significantly ($P$=0.01) higher than the $CBF_{xenon}$ value obtained when 1 MAC of isoflurane was administered alone (33 (3) ISI units). There were no significant differences in rCBF distribution regardless of whether or not isoflurane was given alone or together with nitrous oxide at 0.5 or 1 MAC. In all situations there were higher relative flows in subcortical regions (thalamus and basal ganglia, 10%) and in the pons (7–10% above average). rCBF in the cerebellum was approximately 10% greater than average. In summary, we have found that mean CBF was greater with combined nitrous oxide and isoflurane anaesthesia than previously found with isoflurane alone; however, relative flow distribution was similar. (*Br. J. Anaesth.* 1997; **78**: 407–411).

**Key words**
Anaesthetics volatile, isoflurane. Anaesthetics gases, nitrous oxide. Brain, blood flow. Measurement techniques, tomography.

Nitrous oxide has been used for anaesthesia during neurosurgical procedures for half a century as it was thought to have only little effect on the cerebral circulation.[1 2] However, by the 1970s it was shown that nitrous oxide had marked effects on intracranial pressure (ICP)[3 4] but the literature on the effects of nitrous oxide on the brain is confusing, probably because of species differences, but also because of interactions with other drugs or interventions.[5 6] However, in humans, evidence supporting the conclusion that nitrous oxide is a cerebral vasodilator, in the absence of other interventions, has been obtained previously from cerebral blood flow (CBF) studies.[7–9] Recent studies have shown that nitrous oxide increases blood flow velocity also when it is added to propofol or isoflurane anaesthesia.[10 11] The reason for this vasodilatation is still unknown, but it may theoretically be caused by increased cerebral metabolism[10–13] or by an indirect effect on the cerebral vessels[9 14] as it is known that nitrous oxide is totally inert on isolated human pial arteries.[9]

The aim of this study was to evaluate the effect of isoflurane in combination with 50% nitrous oxide on absolute CBF measured by i.v. $^{133}$xenon[15] combined with recording of the three-dimensional rCBF distribution with SPECT and $^{99m}$Tc-HMPAO in normocapnic patients.

## Patients and methods

We studied 10 male patients, ASA I, undergoing inguinal herniorrhaphy. The study was approved by the Ethics Committee of the Medical Faculty and the Isotope Committee of the University of Lund. Written informed consent was obtained from each participant.

### EXPERIMENTAL PROCEDURE

Ten patients were allocated randomly to one of two groups ($n$=5 in each group), to receive 50% nitrous oxide and 0.5 or 1 MAC of isoflurane during normocapnia. The group who received isoflurane alone also comprised five patients who have been reported

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previously.[16] Subjects in the previous study were anaesthetized with 1 MAC of isoflurane alone, but otherwise treated in the same way as patients in the present investigation.

No premedication was given. Anaesthesia was induced with pethidine 0.75 mg $kg^{-1}$ i.v. and propofol 2–2.5 mg $kg^{-1}$. Suxamethonium 1 mg $kg^{-1}$ was used to facilitate tracheal intubation. Mechanical ventilation was with a Servo ventilator (Siemens 900 C, Siemens Elema, Solna, Sweden). End-tidal carbon dioxide and concentrations of isoflurane were recorded on a Normocap 102-24-02 and a Normac gas monitor (Datex, Helsinki, Finland), respectively. Anaesthesia was maintained with isoflurane and 50% nitrous oxide in oxygen. End-tidal concentrations of isoflurane and carbon dioxide ($PE'_{CO_2}$) were maintained as close as possible to the final experimental condition throughout anaesthesia.

At 10–20 min before the end of surgery, patients were kept anaesthetized with either 0.5 or 1 MAC of isoflurane and 50% nitrous oxide in oxygen for at least 30 min. When stable conditions were achieved and surgery had finished, mean CBF was measured using i.v. radioactive $^{133}$xenon clearance ($CBF_{xenon}$). $^{99m}$Tc-HMPAO was given immediately after the $CBF_{xenon}$ measurement and anaesthesia was maintained for 5 min more. No patient was studied sooner than 60 min after induction of anaesthesia (mean 69 min, range 60–85 min). After a post-anaesthetic recovery period of 1–2 h, patients were brought to the neurophysiological department for SPECT scanning.

During measurement of mean $CBF_{xenon}$, haemoglobin concentration and arterial blood-gas samples were analysed using an ABL 500 (Radiometer, Copenhagen, Denmark). Temperature, heart rate and systemic arterial pressure were monitored throughout the procedure.

### MEASUREMENT OF MEAN CEREBRAL BLOOD FLOW

Mean $CBF_{xenon}$ was measured by injection of 0.5 Gbq (10 mCi) of $^{133}$xenon into a cubital vein, followed by rapid injection of 20 ml of isotonic saline. Uptake and clearance of the tracer substance were recorded with a scintillation detector with wide collimation (approximately 90° view), placed on the right side of the head over the parieto-temporal region, including most of the brain in its field. Clearance through the lungs was recorded from expired air. A Novo Cerebrograph 10a (Simonsen Medical A/S, Randers, Denmark) was used for data collection with a sampling time of 11 min and subsequent flow calculation. $CBF_{xenon}$ was expressed as the initial slope index (ISI)[17] as it represents blood flow of all tissue recorded, but is highly dominated by gray matter blood flow and influenced little by extracerebral components.[17]

### MEASUREMENT OF THREE-DIMENSIONAL CEREBRAL BLOOD FLOW DISTRIBUTION

Regional distribution of CBF was measured by injection of a tracer substance, $^{99m}$Tc- HMPAO 0.5 Gbq (10 mCi) (Ceretec, Amersham, UK) into a cubital vein, followed by rapid injection of 20 ml of isotonic saline. This tracer substance is lipid soluble at the time of injection and is distributed in proportion to blood flow. In brain cells the carrier molecule HMPAO is converted within a few minutes to a water-soluble form which cannot cross the cell membrane. Hence, the amount of $^{99m}$Tc (half-life of 6 h) which remains trapped in the brain cells is proportional to rCBF distribution. Cerebral $^{99m}$Tc distribution was recorded three-dimensionally with a single photon emission computer-aided tomography (SPECT) scanner (Tomomatic 564, Medimatic A/S, Denmark) giving a picture of rCBF distribution at the time of $^{99m}$Tc-HMPAO injection.[18 19] Three-dimensional distribution of $^{99m}$Tc-HMPAO in the brain was recorded in 10 contiguous, approximately 1-cm thick, slices parallel to the orbitomeatal (OM) line, with the centre of the lowest slice located 1 cm below the OM line. The head position was controlled with light beams on the external auditory meatus and the nasion. Slices were recorded in two interlacing sets of five slices each with a recording time of 10 min for each set, which gave approximately $10^6$ counts/slice and an intra-slice resolution of approximately 1 cm. The regions of interest were positioned automatically within each slice, with adjustment to the subject's brain size.

### CALCULATIONS AND STATISTICAL METHODS

The mean $CBF_{xenon}$ value recorded from our detector corresponded to a weighted average of different brain regions, with the weight of each region in the average determined mainly by its $^{133}$xenon content and distance from the detector.[20] Consequently, the $CBF_{xenon}$ value from the parietal detector was an average between CBF in the closest cortical tissue (parietal cortex) and mean CBF, with dominance for the parietal cortex.

In the SPECT $^{99m}$Tc-HMPAO measurements, the average CBF level, calculated as the average number of counts through all regions, gray and white matters, was defined as 100% for presentation of relative flow values. Regions of interest were outlined in the brain slices by a program which was constructed from anatomical templates in a CT brain atlas.[21] Three- dimensional cerebral regions of interest were calculated from adjoining regions of interest in different brain slices representing the same structure. The program gave the mean value in each region of interest and the size of the region of interest.

With the SPECT $^{99m}$Tc-HMPAO measurements, parietal and average CBF had virtually the same value (>>100%) and therefore it was justifiable to approximate the recorded $CBF_{xenon}$ value to parietal cortical CBF. Regional CBF values were calculated from $CBF_{xenon}$ mean flow values and $^{99m}$Tc-HMPAO rCBF distribution, as described by Reinstrup and colleagues.[16] Thus $CBF_{xenon}$ values were equated with parietal values in the regional distribution obtained with SPECT.

The conversion factor from kPa to mm Hg was 0.1333.

All values are given as mean (SEM). Mean

$CBF_{xenon}$ values were tested by factorial design ANOVA, initially on global anaesthesia effects and *post hoc* on the addition of nitrous oxide to isoflurane anaesthesia. Regional CBF ($^{99m}$Tc-HMPAO distribution) was analysed by repeated measures ANOVA with anaesthetic type as between-group factor and regions of interest as within-group factors. $P<0.05$ was considered statistically significant.

## Results

Physiological values of the three groups, at the time of mean CBF measurement, are presented in table 1.

### EFFECTS OF NITROUS OXIDE AND ISOFLURANE ON MEAN $CBF_{XENON}$ USING $^{133}$XENON

There was a significant ($F=5.36$, $P=0.022$ ANOVA) effect on $CBF_{xenon}$ of anaesthesia type. Patients without any surgical stress anaesthetized with 50% nitrous oxide and 0.5 MAC of isoflurane (0.6%) had a mean $CBF_{xenon}$ of 45 (5) ISI units during normocapnia. $CBF_{xenon}$ during isoflurane anaesthesia at 1 MAC (1.2%) and during 50% nitrous oxide did not differ significantly from the flow value with 0.5 MAC (53 (5) ISI units). Compared with 1 MAC of isoflurane alone (CBF=33 (3) ISI units)[16] both $CBF_{xenon}$ values with nitrous oxide in addition to isoflurane were significantly increased ($F=8.16$, $P=0.014$).

*Table 1* Physiological values for the three groups ($n=5$ in each group). Values are mean (SEM or range)

| | $N_2O$+0.5 MAC of isoflurane | $N_2O$+1.0 MAC of isoflurane | 1.0 MAC of isoflurane |
|---|---|---|---|
| Age (yr) | 30 (21–45) | 33 (20–44) | 43 (37–50) |
| $Pa_{CO_2}$ (kPa) | 5.7 (0.1) | 5.8 (0.3) | 5.4 (0.1) |
| $Pa_{O_2}$ (kPa) | 35 (2) | 30 (2) | 32 (8) |
| pH | 7.39 (0.01) | 7.38 (0.02) | 7.41 (0.02) |
| Hb (g litre$^{-1}$ | 146 (6) | 147 (4) | 148 (3) |
| $Temp_{tympanic}$ (°C) | 36.0 (0.1) | 36.2 (0.2) | 35.7 (0.4) |
| MAP (mmHg) | 80 (3) | 76 (3) | 71 (2) |

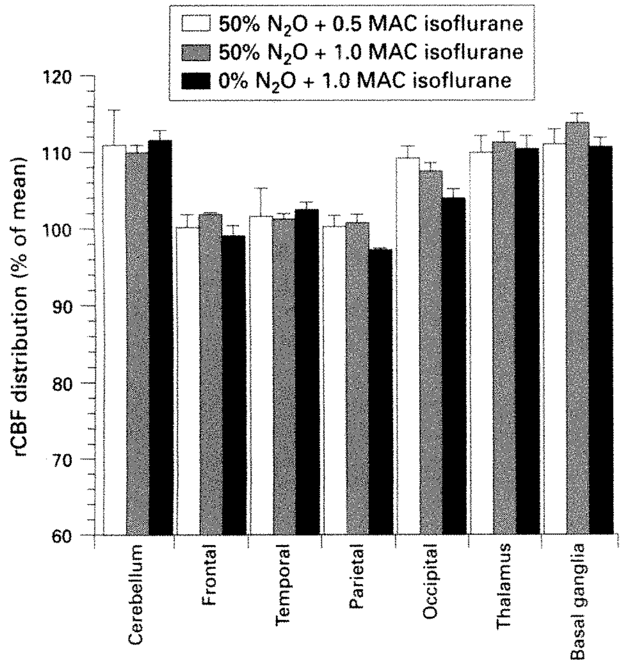

*Figure 1* Regional cerebral blood flow (rCBF) distribution (% of mean relative CBF) during anaesthesia with 50% nitrous oxide and 0.5 MAC of isoflurane, 50% nitrous oxide and 1.0 MAC of isoflurane or 1.0 MAC of isoflurane without nitrous oxide[16] at normocapnia. Results are presented as mean (SEM) ($n=5$ in each group).

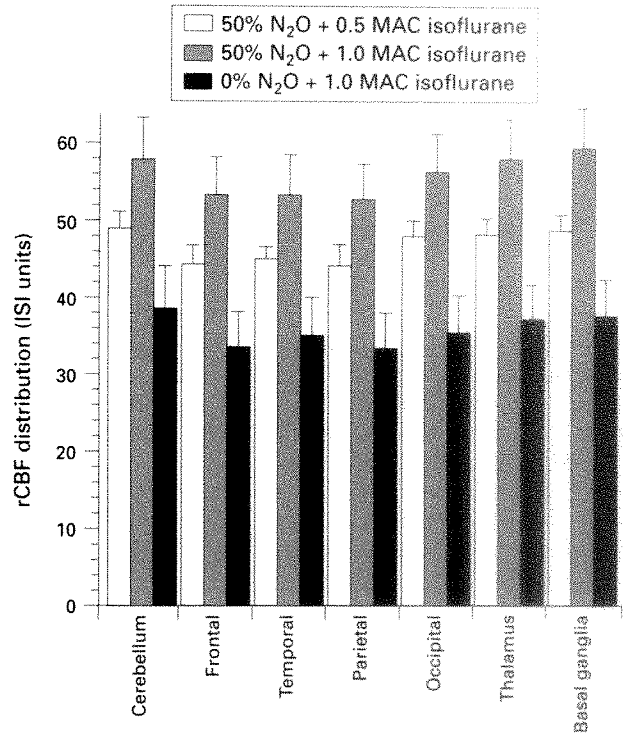

*Figure 2* Regional cerebral blood flow (rCBF) (ISI units) during anaesthesia with 50% nitrous oxide and 0.5 MAC of isoflurane, 50% nitrous oxide and 1.0 MAC of isoflurane or 1.0 MAC of isoflurane without nitrous oxide[16] at normocapnia. Values represent regional distribution recalculated to absolute values (see methods) and are presented as mean (SEM) ($n=5$ in each group).

### EFFECTS OF NITROUS OXIDE AND ISOFLURANE ON THREE-DIMENSIONAL CBF DISTRIBUTION

Nitrous oxide and 0.5 or 1.0 MAC of isoflurane anaesthesia resulted in a pattern with an inhomogeneous CBF distribution ($F=61.6$, $P<0.0001$). During nitrous oxide and isoflurane anaesthesia, the regions with the highest relative CBF were the thalamus, basal ganglia and cerebellum (10% greater than average) followed by the pons (7–10% greater than average). This distribution did not differ from that found during anaesthesia with 1 MAC of isoflurane.[16] rCBF distributions are presented in figure 1.

Absolute rCBF values throughout the same regions were calculated from the two- and three-dimensional blood flow measurements, and are presented in figure 2, together with rCBF values obtained when isoflurane was administered alone.[16]

## Discussion

We have found that anaesthesia during normocapnia with 50% nitrous oxide and 0.5 or 1.0 MAC of isoflurane resulted in a global CBF of 44 and 53 ISI units, respectively. These values were significantly higher compared with a global CBF value of 33 ISI units obtained with 1.0 MAC of isoflurane without nitrous oxide under otherwise identical conditions.[16] This latter CBF value was lower than that in the awake state,[9] which is in accordance with other recent reports[22 23] and contradicts the previous common opinion that isoflurane increases CBF. In contrast, inhalation of 50% nitrous oxide in healthy young men increased global CBF from 55 to 67 ml 100 $g^{-1}$ $min^{-1}$ during normocapnia.[9] This increase in CBF during nitrous oxide administration is in agreement with results from investigations on cortical blood flow in humans.[7 8]

The CBF values found in this study were intermediate between values obtained when nitrous oxide and isoflurane are used alone. The finding that addition of nitrous oxide to a basic anaesthetic increases CBF has been established previously[24 25] using two-dimensional methods. In these studies the effect of nitrous oxide was evaluated by substituting an equipotent dose of volatile anaesthetic in order to maintain an unchanged anaesthetic level. Recent studies have shown that nitrous oxide increases blood flow velocity also when it is added to an otherwise unchanged propofol or isoflurane anaesthesia.[10 11] We found that substituting 0.5 MAC of isoflurane with 50% nitrous oxide increased CBF and that a further, but non-significant, augmentation occurred when the concentration of isoflurane was increased to 1 MAC. Hence, the nitrous oxide-induced effect on blood flow is not attenuated by increasing anaesthetic depth with isoflurane up to 1 MAC. The finding that CBF tended to be higher when the isoflurane concentration was doubled may be explained by a direct vasodilator effect on vascular smooth muscle, caused by increased isoflurane concentrations.[26]

We have reported previously that the global increase in CBF induced by nitrous oxide alone was distributed unevenly, with the main increase in the frontal, temporal and parietal cortex but also in the basal ganglia, insula and in the thalamic region.[9] The flow pattern gave the impression that inhalation of nitrous oxide augmented flow through regions associated anatomically with the limbic system,[27] probably because of selective activation of these areas.[9] This pattern was entirely different from that seen with isoflurane. During 1 MAC of isoflurane anaesthesia, rCBF distribution showed higher CBF levels in the pons and subcortical structures (thalamus and basal ganglia) compared with the cortex.[16] If nitrous oxide stimulates metabolism in some areas of the brain, the effect might be alleviated by addition of other anaesthetics which depress metabolism.[13 28] This fits well with our present finding that nitrous oxide did not alter rCBF distribution induced by isoflurane anaesthesia.

Isoflurane and halothane induced different patterns of rCBF.[16] The reason for the selective difference in relative flow through different regions during isoflurane and halothane anaesthesia is unknown. The most likely explanation is based on the fact that the normal brain has a tight coupling between brain metabolism and flow[29] and that the two volatile anaesthetics have different effects on metabolism in various parts of the brain. A flow metabolism relationship is evident during both isoflurane and halothane anaesthesia in the rat.[30] Assuming that volatile anaesthetics have different effects on metabolism in various brain regions, together with the observations that addition of nitrous oxide to isoflurane increases CBF uniformly and that nitrous oxide has no effect on isolated cerebral arteries,[9] we conclude that our study supports the hypothesis that nitrous oxide exerts an indirect vasodilator effect in the brain.[31] Identification of the mediator(s) of this vasodilator effect merits further investigation.

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# Self-learning fuzzy logic control of neuromuscular block

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## Summary

We have assessed the performance of a "self-learning" fuzzy logic controller to administer atracurium to a required depth of neuromuscular block. We studied 20 ASA I and II patients undergoing surgery anticipated to last longer than 90 min. A Datex Relaxograph was used to measure the degree of neuromuscular block, and control to a T1 twitch height set point of 10% of baseline neuromuscular function was selected. The controller commenced with a blank rule-base and instructed a Graseby 3400 infusion pump to administer an atracurium infusion to maintain this level of block. The system achieved stable control of neuromuscular block with a mean T1 error of −0.52% (SD 0.55%) accommodating a range in mean atracurium infusion rate of 0.25–0.44 mg kg$^{-1}$ h$^{-1}$. These results compare favourably with the more computationally intensive and unwieldy adaptive control strategies for atracurium infusion used previously. There was less variation in infusion rates than in our previously studied fixed rules fuzzy controller. (*Br. J. Anaesth.* 1997; **78**: 412–415).

**Key words**
Neuromuscular block, atracurium. Computers, fuzzy logic.

Provision of reliable neuromuscular block is an important part of modern anaesthetic practice. Newer agents provide rapid onset of dense yet short-acting block providing good conditions for surgery. However, these agents require careful monitoring to reduce the incidence of clinically significant fluctuations in the density of block, and allow rapid offset at the end of surgery. In longer operations multiple incremental doses of neuromuscular blocking agents may be required. Neuromuscular block therefore lends itself to control by continuous drug infusion, but pharmacokinetic and pharmacodynamic differences between patients makes selection of an appropriate infusion rate to maintain the desired level of block difficult.[1]

Closed-loop control provides the ability to maintain stable neuromuscular block while allowing for variation in the individual's response to the drug. This benefits the patient in that the minimum quantity of drug is administered and the clinical workload is reduced, allowing more time to be spent on other aspects of anaesthesia. The reliability of neuromuscular block monitoring with electromyography permits a precise control strategy to be implemented. Various controllers have been demonstrated in the past, from simple on–off type to complex model-based controllers.[2–11] We have demonstrated previously the use of fuzzy logic in the control of neuromuscular block with a fixed rule-base. While this controller provided accurate control of neuromuscular block, we noted considerable variation in blocker infusion rate.[12 13] In addition, such a controller is not adaptive and it is difficult to deduce a general fixed rule to accommodate individual variations between patients. These problems may be overcome by adding a self-learning facility to the controller. Such a controller has been demonstrated previously only in computer simulation.[14 15] This is the first study investigating the clinical use of self-learning fuzzy logic control.

## Patients and methods

The study was approved by the local Ethics Committee and 20 adult ASA I or II patients undergoing surgery anticipated to last longer than 90 min gave written informed consent.

The closed-loop system comprised a general purpose IBM compatible computer (PC) interfaced to a Datex Relaxograph and a Graseby Medical 3400 infusion pump. The PC was programmed to use the "self-learning" fuzzy logic control strategy and coordinate communication via serial links. The system was tested actively by computer simulation in "worst-case" and "noisy-signal" scenarios, and a further check on the adequacy of patient response was implemented to eliminate the possibility of erroneous controller outputs arising should the patient not receive atracurium, for example the infusion catheter became blocked or disconnected. A hierarchical alarm structure was used to deal with alarm conditions appropriately. System hardware and software integrity were tested in real-time using a simulation device attached to the Relaxograph.[16]

Patients received a standard anaesthetic. Anaesthesia was induced with alfentanil 10 μg kg$^{-1}$ and a sleep dose of propofol, followed by an infusion of 10 mg kg$^{-1}$ h$^{-1}$. The patient's lungs were ventilated

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manually with 67% nitrous oxide in oxygen while the automated atracurium delivery system was set up. One arm was placed supine on an extension board and secured with tape. MSB unilect silver–silver chloride electrodes were placed on skin previously cleansed with alcohol solution. The two stimulating electrodes were placed over the ulnar nerve distribution in the forearm, the recording electrodes were placed one on the hypothenar eminence and one at the base of the fifth metacarpal, and the ground electrode was placed on the radial side of the forearm at the wrist. The Relaxograph was then calibrated and set to deliver a train-of-four supramaximal stimulus every 20 s. The Relaxograph was observed for at least 3 min before neuromuscular block was commenced to ensure a stable baseline. We used the first response to train-of-four (T1) as the end-point for monitoring and control. A T1 set point at 10% of baseline was chosen. A filename was entered for data storage and the concentration of atracurium (2 mg $ml^{-1}$) entered so that the computer could convert the controller output from a mass rate to a flow rate, that is ml $h^{-1}$. The patient's weight was entered to enable the loading dose of 0.33 mg $kg^{-1}$ to be calculated, which it then delivered at 1200 ml $h^{-1}$ to facilitate tracheal intubation. Anaesthesia was maintained with propofol 8–10 mg $kg^{-1}$ $h^{-1}$, the patient's lungs ventilated mechanically with oxygen and nitrous oxide, and morphine was administered as appropriate. The fuzzy logic controller maintained neuromuscular block throughout. Recovery of T1 was monitored every 20 s, giving an indication of patient sensitivity to the drug, allowing the controller to create its first control rule. Thus, for instance, if recovery was rapid, a high initial infusion rate was selected as T1 approached 10%, to a maximum rate of 100 mg $h^{-1}$. If T1 failed to decrease below the 10% set point, the computer was programmed to deliver an additional 5-mg bolus and repeat as necessary until T1 was less than 10%. The fuzzy controller commenced operation when T1 had recovered to between 5% and 10%. To reduce spurious data from noisy signals the median of the previous three readings was used. This median T1 value, calculated each 60 s, was then used for action by the controller. In addition, the supervising anaesthetist could administer an atracurium bolus should neuromuscular block be inadequate, alter the T1 set point or quit the programme as required.

The performance of the fuzzy controller was analysed by raw T1 values. T1 errors (measured T1 value − the set point T1 value) were analysed for mean and root mean square deviation (RMSD) for the entire duration of control. In addition, these values were determined for the initial 30 min of control to allow comparison with our previous controller.[12] Mean (SD) atracurium infusion rates delivered every 1 min during control in each individual case were also calculated and then summarized for all 20 patients as mean (SD) and range.

## Results

We studied 20 patients, mean age 43 (range 25–73) yr and mean weight 67 (48–85) kg. Mean duration of control was 75 (46–143) min. Tables 1 and 2 show the control performance indices for both total duration of control and for the first 30 min of control. The mean T1 error from set point was −0.52% (SD 0.55%; range −1.94 to +0.37%) for the total duration of control, and −0.74% (0.73%; −1.80 to +0.90%) for the first 30 min of control. The variation about this mean was low, with a mean SD of 2.3% (0.62%; 1.00–3.61%) for the total duration of

*Table 1* Control performance indices for the total duration of control

| Patient No | Duration of control (min) | Error from set point (%) | | | Atracurium infusion rate (mg $kg^{-1}$ $h^{-1}$) | |
|---|---|---|---|---|---|---|
| | | Mean | SD | RMSD | Mean | SD |
| 1 | 53 | −0.45 | 1.00 | 1.10 | 0.25 | 0.11 |
| 2 | 56 | 0.28 | 2.99 | 3.00 | 0.32 | 0.15 |
| 3 | 79 | 0.37 | 1.67 | 1.71 | 0.36 | 0.10 |
| 4 | 61 | −0.43 | 1.46 | 1.52 | 0.36 | 0.04 |
| 5 | 86 | −0.46 | 2.37 | 2.42 | 0.29 | 0.17 |
| 6 | 64 | −0.97 | 1.97 | 2.20 | 0.35 | 0.23 |
| 7 | 76 | −0.21 | 3.61 | 3.62 | 0.31 | 0.14 |
| 8 | 112 | −0.36 | 3.14 | 3.16 | 0.31 | 0.13 |
| 9 | 57 | −0.08 | 2.13 | 1.87 | 0.36 | 0.16 |
| 10 | 134 | −0.48 | 2.22 | 2.27 | 0.38 | 0.22 |
| 11 | 143 | 0.33 | 1.97 | 2.00 | 0.27 | 0.08 |
| 12 | 65 | −0.82 | 1.90 | 2.07 | 0.30 | 0.12 |
| 13 | 36 | −1.24 | 2.35 | 2.65 | 0.28 | 0.10 |
| 14 | 53 | −0.34 | 2.20 | 2.23 | 0.32 | 0.08 |
| 15 | 39 | −1.04 | 2.60 | 2.80 | 0.42 | 0.22 |
| 16 | 63 | −0.52 | 1.91 | 1.98 | 0.44 | 0.12 |
| 17 | 65 | −0.50 | 2.15 | 2.21 | 0.30 | 0.12 |
| 18 | 112 | −1.94 | 3.15 | 3.69 | 0.35 | 0.32 |
| 19 | 63 | −0.47 | 2.49 | 2.53 | 0.38 | 0.15 |
| 20 | 86 | −0.97 | 2.62 | 2.80 | 0.35 | 0.13 |
| Mean | 75.15 | −0.52 | 2.30 | 2.39 | 0.34 | 0.14 |
| SD | 29.36 | 0.55 | 0.62 | 0.66 | 0.05 | 0.06 |
| Range | 36–143 | −1.94–0.37 | 1.00–3.61 | 1.10–3.69 | 0.25–0.44 | 0.04–0.32 |

*Table 2* Control performance indices for the first 30 min of control

| Patient No. | Error from set point (%) |  |  | Atracurium infusion rate (mg kg$^{-1}$ h$^{-1}$) |  |
|---|---|---|---|---|---|
|  | Mean | SD | RMSD | Mean | SD |
| 1 | −0.67 | 1.23 | 1.40 | 0.27 | 0.14 |
| 2 | −1.49 | 3.11 | 3.45 | 0.33 | 0.21 |
| 3 | 0.89 | 2.20 | 2.38 | 0.38 | 0.13 |
| 4 | −1.05 | 1.75 | 2.04 | 0.37 | 0.04 |
| 5 | 0.14 | 2.76 | 2.76 | 0.29 | 0.15 |
| 6 | −1.29 | 2.26 | 2.60 | 0.37 | 0.24 |
| 7 | −0.51 | 2.36 | 2.41 | 0.41 | 0.10 |
| 8 | −1.38 | 2.83 | 3.15 | 0.38 | 0.12 |
| 9 | −0.36 | 2.35 | 1.83 | 0.35 | 0.18 |
| 10 | −0.66 | 2.80 | 2.88 | 0.48 | 0.22 |
| 11 | 0.63 | 2.59 | 2.67 | 0.24 | 0.11 |
| 12 | −1.59 | 1.79 | 2.39 | 0.32 | 0.14 |
| 13 | −0.78 | 2.27 | 2.40 | 0.30 | 0.10 |
| 14 | −0.67 | 2.24 | 2.33 | 0.31 | 0.10 |
| 15 | −1.73 | 2.47 | 3.00 | 0.42 | 0.22 |
| 16 | −1.75 | 1.90 | 2.57 | 0.46 | 0.15 |
| 17 | −0.28 | 2.61 | 2.62 | 0.31 | 0.16 |
| 18 | −0.70 | 5.02 | 5.07 | 0.44 | 0.44 |
| 19 | −0.44 | 2.78 | 2.81 | 0.39 | 0.17 |
| 20 | −1.04 | 2.89 | 3.04 | 0.30 | 0.08 |
| Mean | −0.74 | 2.51 | 2.69 | 0.36 | 0.16 |
| SD | 0.73 | 0.75 | 0.73 | 0.07 | 0.08 |
| Range | −1.80–0.90 | 1.20–5.0 | 1.40–5.10 | 0.27–0.48 | 0.04–0.44 |

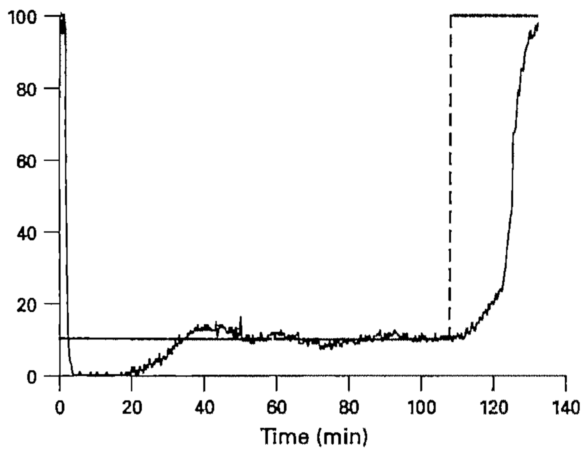

*Figure 1* Sample clinical trace obtained with self-learning fuzzy controller showing stable neuromuscular block at the 10% level over 75 min. ——=Desired T1 value, ——=raw T1 values.

control and 2.51% (0.75%; 1.20–5.00%) for the first 30 min. Mean RMSD values were similar to the mean SD, being 2.39% (0.66%; 1.10–3.69%) for the total duration of control, and 2.69% (0.73%; 1.40–5.10%) for the first 30 min, confirming that mean error was close to zero. Figure 1 shows a sample clinical trace.

Mean atracurium requirements varied from 0.25 to 0.44 mg kg$^{-1}$ h$^{-1}$ for the total duration of control and from 0.27 to 0.48 mg kg$^{-1}$ h$^{-1}$ for the first 30 min. The SD of the infusion rates of atracurium delivered over the period of control gives an indication of the variation in infusion rate for that period in each patient. The mean SD atracurium infusion rate was 0.14 mg kg$^{-1}$ h$^{-1}$ for the total duration of control and 0.16 mg kg$^{-1}$ h$^{-1}$ for the first 30 min. In all cases good operating conditions prevailed throughout and all neuromuscular block was antagonized easily at the end of surgery. No patient required a bolus dose of atracurium to maintain adequate neuromuscular block.

## Discussion

Fuzzy logic is an appropriate, simple and effective technique for controlling non-linear and unpredictable processes, dealing in imprecise, qualitative (i.e. "fuzzy") terms such as "low", "medium" or "high" rather than precise measurements.[17 18] This imprecision permits very simple but effective control rules to be generated which are easy to modify and update rapidly in real-time. Fuzzy logic control is intrinsically suited to the control of physiological processes because it requires little hard input data before it can begin functioning, unlike other strategies such as "neural networks".

For closed-loop control of neuromuscular block the following features need to be addressed when designing the system: recognition of the onset and, more importantly, the rate of decay of neuromuscular block; recognition of the difference between desired and actual T1 value (error); recognition of the rate of change in error from the desired T1 value; and elimination of drift from the desired T1 value when achieved, that is steady state error.

Using a fixed rule-base, we have demonstrated previously that fuzzy logic control is appropriate for controlling neuromuscular block.[12] However, the development of such a controller required the construction of a hand-crafted rule-base which was time and labour intensive. However, by incorporating a "self-learning" layer to the fuzzy controller, it becomes self-teaching in real-time in the clinical situation and dispensed with the need for a pre-set fixed rule-base. Our self-learning controller starts with a blank rule-base, and this is the first study to investigate the clinical application of such an intelligent control technique.

The "self-learning" strategy implemented in our controller functioned by rapidly and repeatedly measuring T1 twitch height and modifying the atracurium infusion rate. This allowed the controller to recognize the patient's drug requirements and select infusion rates appropriate to maintain 90% neuromuscular block. Initially, the fuzzy rule-base is completely blank as the controller is unaware of its first rule until control begins. This first rule is simple and generated by assessing the return of neuromuscular tone towards the desired T1 height. The effect is then assessed and adapted by generating new rules as control continues. This is achieved by adding a performance index which measures the error from a desired trajectory and modifies recently generated control rules so making the controller self-learning. In addition an ageing process was added to the rules generated so that those recently generated carried more weight, or were considered "more relevant" than older rules. This helps eliminate steady state error and continually improves controller performance.

The results of this study showed improved performance over previous controllers. Control was as good as our previous fixed-rule controller with less erratic infusion rates being demanded; the controller delivered a mean SD atracurium infusion rate of 0.16 mg $kg^{-1}$ $h^{-1}$ for the first 30 min compared with 0.23 mg $kg^{-1}$ $h^{-1}$ in our previous study.[12] Control was implemented with a basic amount of information. At no point did the controller have to administer a bolus in order to regain control of a deteriorating situation and in no case was a diverging or progressively unstable oscillation entered.

While fuzzy logic has been used in other fields in anaesthesia[17–19] this is the first occasion where, by application of a self-learning facility to the fuzzy logic controller, a physiological process during anaesthesia has been controlled entirely by machine alone. The controller determined individual drug requirements and administered atracurium accurately in each case, demonstrating the ability to assess and respond to fluctuating patient conditions during surgery. The success of this self-learning control system should encourage research into the control of other physiological processes.

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REVIEW ARTICLE

# Congenital heart disease in adults

D. FINDLOW AND E. DOYLE

Congenital anomalies of the heart and cardiovascular system occur in 7–10 per 1000 live births (0.7–1%).[113] It is the commonest form of congenital disease and accounts for approximately 30% of the total burden of congenital disease. With a decline in the incidence of rheumatic heart disease, congenital heart disease has become the main cause of heart disease in children in the developed world; 10–15% of affected children have associated congenital anomalies of the skeletal, genitourinary or gastrointestinal systems. Approximately 10–15% of patients with congenital heart disease may survive untreated to adulthood but the majority require some form of cardiac surgery as children. Nine lesions comprise more than 80% of congenital heart disease while a wide range of more unusual and complex lesions comprise the remainder.

*Table 1* Incidence of common congenital heart defects[66]

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|---|---|
| Acyanotic lesions | |
| Ventricular septal defect | 35% |
| Atrial septal defect | 9% |
| Patent ductus arteriosus | 8% |
| Pulmonary stenosis | 8% |
| Aortic stenosis | 6% |
| Coarctation of the aorta | 6% |
| Atrioventricular septal defect | 3% |
| Cyanotic lesions | |
| Tetralogy of Fallot | 5% |
| Transposition of the Great Arteries | 4% |

Surgical closure of a patent ductus arteriosus was first performed in 1939.[53] In 1945 the first surgical repair of coarctation of the aorta was reported[27 54] and the Blalock–Taussig shunt from the left subclavian to the left pulmonary artery was introduced as a palliative procedure for tetralogy of Fallot[12] allowing patients with this lesion to live for several decades. In 1955 a series of patients who underwent successful open heart surgery with cardiopulmonary bypass to correct septal defects was reported.[75]

Advances in cardiological diagnosis and management, surgical techniques, anaesthesia and intensive care have resulted in a situation where the majority of conditions are operated up on with a high proportion of medium-term survivors. It has become increasingly apparent that few of these procedures are corrective, resulting in a totally normal heart, but that the majority are palliative to a greater or lesser extent and that there are long-term residual effects from these procedures. The ligation and division of an asymptomatic patent ductus arteriosus is closest to a complete cure. Consistent features of surgery for congenital heart disease include low early mortality, good medium term survival with a high proportion of asymptomatic patients but a high incidence of longer term problems relating to the original condition and to the pathophysiological effects of the operative procedure. These may only become apparent in an exercising or stressed patient as occurs during trauma, infection, surgery or the postoperative period.

A large cohort of patients with treated congenital heart disease is now surviving into adult life. Ideally these patients should undergo regular review by a cardiologist to detect developing problems but this may fall by the wayside as adolescents become adults, move home, travel and assert independence by defaulting on appointments. There are profound implications for these people in relation to life insurance, employment prospects, genetic counselling, pregnancy and exercise. These individuals now approaching adolescence and adult life may require anaesthesia for elective and emergency surgery, trauma and childbirth. They have traditionally returned to paediatric cardiac centres for noncardiac surgery but as they become adults this is not feasible and they must be anaesthetized in adult hospitals. Cardiovascular impairment in these patients is generally the result of one or more pathophysiological processes which are the result of a multitude of anatomical abnormalities. These are arrhythmias, hypoxaemia, pulmonary disease and ventricular dysfunction.

In the past, unoperated significant congenital heart disease in adults was not uncommon but it is now unusual for this to be seen, and some form of correction or palliation is usually performed in childhood or adolescence. Those untreated lesions which may be seen in adults will have initially caused few or no symptoms but these develop in later life because of calcification of abnormal valves, onset of arrhythmias,

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Heart, congenital defects. Complications, congenital heart disease. Surgery, cardiovascular.

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progressive ventricular dysfunction, pulmonary hypertension or infective endocarditis. Patients who undergo insertion of artificial patches, conduits or valves as children usually deteriorate and require reoperation when older because of lack of growth and structural deterioration of the implant.

## General considerations

### ARRHYTHMIAS

Arrhythmias are possibly the commonest problem in long-term survivors of surgery for congenital heart disease. Atrial arrhythmias are common after atrial surgery and in the presence of atrial distension, as after a Fontan procedure. Right ventriculotomy entails damage to conducting tissue and often results in a right bundle branch block pattern in the ECG. This is usually asymptomatic but when combined with left bundle damage resulting in left bundle hemiblock may progress to complete heart block. Preoperative 24-h ambulatory ECG recording is indicated in symptomatic patients undergoing elective surgery.

### HYPOXAEMIA

Residual hypoxaemia may be caused by decreased pulmonary perfusion with residual right-to-left shunts or by pulmonary hyperperfusion. With limited or obstructed pulmonary blood flow, strategies to avoid further hypoxaemia during anaesthesia include ensuring adequate hydration, maintaining systemic arterial pressure (to minimize right-to-left shunting), minimizing increases in pulmonary vascular resistance (hypocapnia, alkalosis, hyperoxia, low mean airway pressure) and avoiding sudden increases in oxygen requirements caused by inadequate anaesthesia. In the case of pulmonary hyperperfusion with mixing of systemic and pulmonary venous blood, increases in the pulmonary to systemic flow ratio (*Qp*/*Qs*) either increase cardiac work or, if ventricular function is already maximal, decrease systemic perfusion. Persisting left-to-right shunts also predispose to chest infections and worsening of existing ventilation–perfusion abnormalities. Theoretical considerations suggest that in the presence of a right-to-left shunt, inhalation induction of anaesthesia is slower and intravenous induction more rapid than normal while left-to-right shunts have opposite effects. In practice these factors have no significant clinical effect on induction of anaesthesia.

Hypoxaemia results in polycythaemia, limitation of maximal exercise capacity and a tendency to vascular thrombosis. The ability to increase cardiac output in response to exercise or stress is reduced. Possible mechanisms for myocardial dysfunction include recurrent episodes of severe hypoxaemia, decreased coronary perfusion pressure secondary to systemic pulmonary artery shunting and increased blood viscosity leading to microvascular occlusion. These factors result in myocardial ischaemia and fibrosis and these changes are a common post-mortem finding even in affected infants. Ultimately, ventricular diastolic compliance is reduced and a greater ventricular end-diastolic volume is required to maintain stroke volume, resulting in reduced myocardial reserve or ventricular failure. Children undergoing correction of hypoxic lesions such as tetralogy of Fallot after 2 yr of age commonly have normal left ventricular function at rest but reduced ability to increase cardiac output in response to exercise,[15] suggesting that chronic hypoxaemia is associated with irreversible myocardial damage.

Polycythaemia is the main adaptive response to chronic hypoxaemia and is necessary to provide adequate tissue oxygenation. Red cell mass may be up to three times normal and blood volume may exceed 100 ml $kg^{-1}$. A normal haemoglobin concentration during an acute illness may indicate bleeding or iron deficiency. Dehydration and loss of extracellular fluid aggravates this tendency. Blood viscosity is increased and associated with an increased risk of thrombosis and intracranial haemorrhage. Hypoxaemia and polycythaemia are associated with abnormal haemostasis in patients with congenital heart disease. The aetiology of this effect is unclear but includes thrombocytopenia, platelet dysfunction, hypofibrinogenaemia, accelerated fibrinolysis and factor deficiencies. Patients may exhibit easy or spontaneous bruising, epistaxis and haemoptysis. Prolongation of the bleeding time, thrombin time and partial thromboplastin time may be seen. Aspirin, non-steroidal anti-inflammatory drugs and heparin may exacerbate these effects. The risk of excessive perioperative bleeding is increased.

### PULMONARY HYPERTENSION

Unrestricted left-to-right shunts which result in increased pulmonary blood flow prevent the normal postnatal decreases in pulmonary blood flow, pulmonary vascular resistance and pulmonary artery pressure. Examples of this include large unrestrictive ventricular septal defects, atrioventricular canal defects, transposition of the great arteries with ventricular septal defect and a large patent ductus arteriosus. These lesions produce pulmonary hypertension and right ventricular hypertrophy early in life. If this situation continues there is the development of irreversible pulmonary hypertension which in many cases does not regress fully after surgical repair. The desire to prevent the development of irreversible pulmonary hypertension is one of the reasons for progressively earlier definitive repair of these lesions being undertaken. Even after repair a patient with significant preoperative pulmonary hypertension may present problems when undergoing non-cardiac surgery under general anaesthesia. With other lesions such as untreated atrial septal defect where pulmonary flow is increased and pressures are normal, pulmonary vascular disease takes decades to develop and is rarely an issue in the post-repair management of anaesthesia.

The aim in patients at risk is to maintain right ventricular performance in the face of increased right ventricular afterload. Predisposing factors should be avoided and this may also reverse any reversible component to the hypertension. These include hypoxaemia and hypercapnia, acidosis, atelectasis, hyperinflation or physical compression of the lungs. Patients should be adequately premedicated and anaesthetized to avoid unnecessary sympathetic stimulation. Whenever possible regional anaesthetic techniques are suitable in these circumstances to avoid predisposing factors. For all but the briefest cases performed under general anaesthesia, tracheal intubation and intermittent positive pressure ventilation should be used to ensure adequate oxygenation and avoid hypercapnia and acidosis. Mild respiratory alkalosis should be produced. Adequate depth of anaesthesia before intubation is essential to avoid reflex pulmonary vasoconstriction. After operation, the same principles apply and also include measures to provide adequate analgesia. Preload may be assessed by central venous pressure monitoring, and the use of a pulmonary artery catheter (if the anatomy allows) is useful and permits accurate measurements and evaluation of treatment during anaesthesia and the postoperative period in patients at risk. Inotropic support of the heart may improve right ventricular performance until the situation improves and vasodilators with a degree of selectivity for the pulmonary circulation such as tolazoline and prostacyclin are effective pulmonary vasodilators,[95 106] although the disadvantages of systemic hypotension and thrombocytopenia have limited their use. Recent interest in the use of inhaled nitric oxide as a pulmonary vasodilator in several conditions has been rewarding and this is now a valuable treatment for pulmonary hypertension. It is particularly useful to have a treatment which does not simultaneously lower systemic vascular resistance and increase the degree of right-to-left shunting. Nitric oxide, in concentrations up to 80 parts per million, has been used to treat pulmonary hypertension in congenital heart disease,[98] after cardiac surgery,[98 122] in primary pulmonary hypertension,[91] persistent pulmonary hypertension of the newborn[69 99] and the adult respiratory distress syndrome.[102]

### SHUNTS

Classical Blalock–Taussig shunts performed using the subclavian artery result in loss of radial pulsation in the left arm and the inability to measure arterial pressure here or insert an intra-arterial cannula. Occasionally patients have a classical or modified Blalock–Taussig shunt as the only or main source of pulmonary perfusion. In this case pulmonary perfusion and oxygenation of blood depends on the physical characteristics of the shunt, mainly its length and diameter. As these are fixed and pulmonary artery pressure is usually low relative to systemic arterial pressure, pulmonary blood flow is dependent primarily on systemic arterial pressure which drives blood through the shunt. These patients are hypoxaemic and polycythaemic with a predisposition to thrombosis. Measures which lower systemic arterial pressure or systemic vascular resistance may have disastrous effects on pulmonary perfusion and should be used with caution.

### THROMBOSIS AND EMBOLI

In patients with residual connections between the right and left sides of the heart, paradoxical embolism of air or clot to the central nervous system, mesenteric circulation, renal circulation and skeletal vessels may occur during anaesthesia and surgery. Thromboses may occur during the postoperative period and are particularly worrying if there are areas in the heart likely to cause thrombus or if there is a significant right-to-left shunt.

### ANTIBIOTIC PROPHYLAXIS

Infective endocarditis remains a risk after pulmonary or aortic valvotomy, repair of tetralogy of Fallot and most complex operations, especially if artificial material is inserted. It is not a risk after simple repair of atrial septal defect, ventricular septal defect or patent ductus arteriosus. The risk is present during delivery, and labouring women with relevant lesions should receive antibiotic prophylaxis until after delivery.

### ANAESTHETIC TECHNIQUE

In many cases where there has been a good outcome from cardiac surgery and where there is no evidence of late deterioration, conventional anaesthetic management is suitable. In more complex cases with functional limitation, the details of the anaesthetic technique chosen are likely to be less important than the care with which the patient is managed. Modification of the anaesthetic technique to take account of the main problems currently presented by the patient is required. In general, adequate premedication is desirable to avoid anxiety and tachycardia. Slow incremental induction of general anaesthesia and the avoidance of myocardial depression, vasodilatation and hypotension are particularly important in patients where there is myocardial dysfunction or where myocardial performance is critically dependent on preload, as in cavo–pulmonary anastomoses and some atrial switch procedures. In most compromised patients undergoing general anaesthesia, tracheal intubation and intermittent positive pressure ventilation should be used for all but the shortest procedures to avoid the potential complications of transient hypoxaemia or hypercapnia and respiratory acidosis. There should be a low threshold for the use of invasive cardiovascular monitoring, although this may be difficult to perform if there has been previous cannulation of arteries and central veins. Invasive monitoring of central venous pressure is particularly valuable in detecting changes in preload and for guiding fluid replacement in those patients who require a high central venous pressure to ensure pulmonary perfusion or who have a morphological pulmonary ventricle acting as the systemic ventricle. It is also valuable for similar reasons during central neuraxial regional techniques. An arterial catheter provides continuous arterial pressure measurement in patients who may suffer arrhythmias, increased right-to-left shunting and hypoxaemia or reduced cardiac output if arterial pressure decreases with hypovolaemia or vasodilatation.

Regional anaesthetic techniques should be considered alone and combined with general anaesthesia whenever possible. In many circumstances the opportunity to avoid general anaesthesia and perform the proposed procedure in an awake or lightly sedated patient will avoid many potential problems. The excellent postoperative analgesia which is often a feature of regional techniques reduces cardiovascular stress and the release of catecholamines, which may cause arrhythmias and pulmonary vasoconstriction. There is considerable evidence from obstetric practice that lumbar extradural block may be performed safely even in severely compromised patients if the block is produced slowly and incrementally, invasive monitoring is used to guide fluid administration and vasodilatation and hypotension are avoided.

## Specific conditions

### PATENT DUCTUS ARTERIOSUS

Ligation of a small patent ductus arteriosus in an asymptomatic child is probably the only surgical procedure for congenital heart disease which results in an entirely normal individual without any long-term complications. An untreated small patent ductus arteriosus has a mortality of more than 40% by the age of 50 yr and is prone to bacterial endocarditis (more accurately endarteritis of the pulmonary artery). A larger duct often results in increased pulmonary vascular resistance and volume overload of the left ventricle. These changes may not entirely regress after ligation of the duct and there may be long-term pulmonary hypertension. Ducts may also be closed via the transvenous route using a cardiac catheter.[6]

### ATRIAL SEPTAL DEFECT

The ostium secundum form of atrial septal defect is caused by failure of closure of the foramen ovale. The majority of cases are detected in childhood and repaired before any long- term sequelae develop. If untreated the risks of death are 25% by 27 yr, 50% by 36 yr, 75% by 50 yr and 90% by 60 yr.[18] The long-term prognosis after repair is excellent. In patients without arrhythmias before closure there is a low incidence of late postoperative arrhythmias (5–10%). In patients treated after the onset of atrial fibrillation or flutter, these rhythms reappear in virtually all patients by 25 yr after repair. More rarely nodal bradycardias or complete heart block may occur. Endocarditis does not occur on the repaired defect and is seen only if there are associated left-sided anomalies such as a cleft mitral valve.

Atrial septal defects which have appropriate anatomical features especially an adequate rim of septal tissue, may be repaired by a transvenous approach in the cardiac catheter laboratory using a clamshell transcatheter device.[16] This avoids the need for sternotomy and cardiopulmonary bypass and may prove superior in long-term follow-up studies. These devices become covered in endothelium, and antibiotics for the prophylaxis of endocarditis are not subsequently required unless there is a residual defect with exposed foreign material or a residual defect and shunt with turbulent blood flow. There are currently no data comparing the incidence of long-term complications after the two procedures.

### VENTRICULAR SEPTAL DEFECT

Ventricular septal defect is the commonest congenital cardiac malformation (35%) and occurs both as an isolated defect and as part of more complex anomalies. They are most commonly of the membranous or perimembranous type and lie posterior and superior to the crista intraventricularis in what would be the membranous portion of the ventricular septum. The bundle of His lies at the posterior margin of this defect and may be damaged during surgical repair. In 10% of isolated congenital ventricular septal defects there are multiple defects in the muscular portion of the septum. These may be seen in an adult after repair of a membranous ventricular septal defect as they are difficult to close completely at the time of surgery because of heavy trabeculation on the right ventricular aspect of the interventricular septum. As these muscular lesions are small they rarely lead to increased right ventricular or pulmonary artery pressure and leaving them unrepaired may be safer than persisting with attempts at closure. Persisting defects of this nature carry the risk of endocarditis and systemic paradoxical embolism of air or clots during the perioperative period. Occasionally, a small asymptomatic ventricular septal defect is left unrepaired (maladie de Roger) and this does not have any haemodynamic consequences but the risk of endocarditis and paradoxical embolism remains.

Traditional surgical closure of a ventricular septal defect via a right ventriculotomy is associated with an incidence of 15–100% of subsequent conduction abnormalities, especially right bundle branch block and left axis deviation.[51 87] Progression to third-degree (complete) atrioventricular block may occur especially if there was a transient period of complete heart block in the early postoperative period.[51] Ventricular ectopics and ventricular tachycardia may also occur. The incidence of these problems is lower in patients who have undergone closure of a ventricular septal defect via a right atrial approach rather than via a right ventriculotomy but they may still occur presumably because of damage to the right bundle close to the defect.[87] Pulmonary hypertension may not regress completely after repair in affected patients and particularly during exercise this may become severe so that ultimately pulmonary vascular disease becomes established and irreversible.

### AORTIC STENOSIS

This comprises 5% of congenital heart disease and is found in association with other lesions, especially coarctation of the aorta, in approximately another 5%. Aortic valve replacement in children is fraught with difficulty and is avoided whenever possible. Because of this, treatment is usually by means of an aortic valvotomy. This procedure results in improvement of the stenosis but usually at the price of some degree of regurgitation. Symptoms tend to recur as the child grows and valve replacement may eventually be necessary because of this or worsening aortic regurgitation. Patients may be well for many years until deterioration occurs and may undergo anaesthesia along the same principles as older patients with aortic valve disease. Endocarditis remains a significant risk.

### PULMONARY STENOSIS

This condition comprises approximately 8% of congenital heart disease. Treatment in severe cases was by open valvotomy but in recent years this has been replaced by balloon valvuloplasty.

### TETRALOGY OF FALLOT

The tetralogy of Fallot consists of a large ventricular septal defect with right ventricular outflow tract obstruction which is either valvular, infundibular or both. The two other features which make up the tetralogy are right ventricular hypertrophy and overriding of the interventricular septum by a dilated aorta. Although this lesion is compatible with survival to adulthood, the majority of cases are detected and repaired in childhood.

Traditional surgical management of tetralogy of Fallot was by means of a systemic pulmonary artery Blalock–Taussig shunt in symptomatic neonates and infants, followed by definitive repair at 2–5 yr of age or in asymptomatic patients definitive repair at the same stage with no prior shunt. Surgical correction consists of closure of the ventricular septal defect and relief of the pulmonary stenosis. This is usually performed by incision of the right ventricular outflow tract and pulmonary artery, resection of hypertrophic muscle bands and, if necessary, placement of a transannular patch of pericardium or Dacron over the incised pulmonary valve ring and proximal pulmonary artery. Recently, transatrial repair has been developed where, if the anatomy is appropriate, the ventricular septal defect may be closed via the right atrium without the need for a ventriculotomy. The two-stage policy is associated with the problems of chronic hypoxaemia for several years, right ventricular hypertrophy leading to subsequent ventricular dysfunction and the potential complications of a Blalock–Taussig shunt which include shunt failure, pulmonary artery narrowing, pulmonary artery distortion and the development of pulmonary artery vascular occlusive disease.

In order to avoid these problems definitive correction in infancy has now become common and can be achieved with a low mortality in infants of less than 12 months.[21 56 117] This approach avoids the need for two cardiac operations and eliminates the complications of pulmonary artery shunting. In the fetus with tetralogy of Fallot the right ventricle functions against placental resistance as normal and there is a normal right ventricular pressure and compliance despite right ventricular outflow tract obstruction. Successful repair early in life, therefore, has the potential to avoid the development of right ventricular hypertrophy and dysfunction which is implicit in tetralogy of Fallot. There is also the theoretical advantage that this aggressive approach may minimize secondary damage to heart, lungs and brain of a prolonged period of chronic hypoxaemia until definitive repair. Early correction is considered to improve cumulative survival, reduce complications and enhance later quality of life with better late results than repair performed in later childhood.[15 120] The incidence of late ventricular arrhythmias is certainly lower in patients who undergo repair early in life. This is probably related to the progressive right ventricular hypertrophy and fibrosis which develops in uncorrected tetralogy of Fallot.[30] An initial palliative shunt in infancy followed by definitive repair several years later is still indicated in symptomatic patients of weight less than 3 kg, the presence of major associated anomalies or unfavourable patterns of pulmonary artery anatomy.

The results of surgery are generally good with most patients attaining near normal functional capacity.[58 59 129] The overall 30-yr survival rate in hospital survivors for a large series was 86% compared with a rate of 96% in a control population. Intracardiac repair performed at more than 12 yr of age carries a significantly worse prognosis than earlier repair.[83] Late sequelae include supraventricular tachyarrhythmias, ventricular arrhythmias,[57] right-sided heart failure resulting from ventriculotomy, pulmonary regurgitation and reduced exercise tolerance.[20 83 100]

Evaluation of pulmonary function 13–26 yr after surgery in 68 patients who had undergone definitive intracardiac repair of tetralogy of Fallot demonstrated moderately reduced work capacity and lung function. In particular, forced vital capacity, maximum voluntary ventilation and symptom-limited work capacity were approximately 80% of predicted.[65] Other long-term follow-up studies have demonstrated reduced exercise tolerance, reduced diffusing capacity, increased physiological dead space and increased alveolar–arterial oxygen tension differences after late definitive repair possibly secondary to pulmonary vascular disease.[115 123] There was no tendency to normalization of work capacity or lung function over two decades of follow-up. Exercise capacity tends to be related inversely to age at the time of definitive repair.[60] A late age at repair implies several years of pulmonary hypoperfusion which may have contributed substantially to the pulmonary damage and this may not occur in patients currently undergoing early definitive intracardiac repair. Residual pulmonary regurgitation with increased right ventricular stroke volume after repair is strongly correlated with reduced vital capacity and respiratory reserve and with reduced exercise capacity.[103 124] Patients who had not undergone palliative Blalock–Taussig shunt had better lung function at follow-up than those who had, but the shunt may not have been the entire cause of reduced lung function as shunted patients tend to be smaller with more severe disease. Reduced lung function associated with Blalock–Taussig shunts may be caused by hypoplasia of the lung, impaired ventilatory mechanics, hypoperfusion, increased blood viscosity, thrombosis and occlusion of small vessels. Alternatively there may be pulmonary hyperperfusion through a shunt which is too wide causing intimal thickening and pulmonary hypertension.

Cardiac output in relation to oxygen consumption was reduced in 74% of patients during exercise, and symptom-limited exercise tolerance was 87% of predicted.[64] Right ventricular pressure was uniformly high during exercise compared with normal. Work capacity is affected adversely by right ventricular hypertension and pulmonary regurgitation. Residual right ventricular hypertension is associated with ventricular arrhythmias and late sudden death.[46 80] The use of a transannular patch to relieve right ventricular outflow tract obstruction is significantly associated with a high incidence (58%) of pulmonary regurgitation, right ventricular dilatation and dysfunction. These features are strongly correlated with decreased exercise capacity.[20 80]

Arrhythmias are common after repair as a consequence of the proximity of the conduction system to the operative field. There is an increased risk of sudden death and this occurs in 0.3–5% of subjects by 16 yr after operation.[22 30 46 120 129] Ventricular ectopics are present in 40–50% of adult survivors of tetralogy of Fallot repair. The frequency and complexity of ventricular ectopics increases with increasing age.[100] Risk factors for ventricular ectopics are older age at the time of repair, incomplete palliation as demonstrated by right ventricular pressure or volume overload, ventricular dysfunction and pre-existing arrhythmias. Supraventricular and ventricular arrhythmias were found in 72% of patients on 24-h ECG a mean of 14 yr after repair. In 43 asymptomatic patients who underwent exercise testing between 1 and 14 yr after repair, premature ventricular ectopics were recorded during exercise in 23% of subjects; 50% of these had multifocal ventricular ectopics and there were occasional short runs of ventricular bigeminy or of ventricular tachycardia.[60] Ventricular tachycardia occurring after repair of tetralogy of Fallot arises from the ventriculotomy site or from the repaired ventricular septum which are both potential sites of fibrosis and scarring.[57] Right bundle branch block is present in more than 90% of subjects.[120] Left anterior hemiblock combined with right bundle branch block has been reported in up to 10% of subjects after repair. The early prognosis of this combination is favourable but long-term progression to complete heart block is likely.[37] On the basis of these findings it has been suggested that patients undergoing elective surgery should undergo preoperative exercise testing or 24-h Holter monitoring to unmask ventricular arrhythmias so that appropriate treatment may be commenced in patients with frequent episodes. In patients with evidence of advanced atrioventricular block temporary pacing may be advised during the perioperative period. It is clear that after surgical correction of tetralogy of Fallot asymptomatic patients often have significant lesions which may affect cardiac and respiratory function, require surveillance and which may need future interventions.

Patients may occasionally be seen with tetralogy of Fallot who have had a Blalock–Taussig shunt but no subsequent definitive correction. These patients are chronically hypoxaemic and polycythaemic. Some 10% die each 5 yr[32] and the 15-yr mortality in one series of 845 patients was 36%.[59] Life-threatening events include intracerebral abscess in 5%, other cerebrovascular complications particularly thrombotic stroke in 5%, and infective endocarditis in 30%.[32 96]

### TRANSPOSITION OF THE GREAT ARTERIES

Transposition of the great arteries refers to a condition in which the aorta arises from an anatomical right ventricle and the pulmonary artery from an anatomical left ventricle. The transposed aorta usually lies in an anterior plane compared with the pulmonary trunk. The term malposition may be used if there is only one ventricle or if both arteries arise from one of two ventricles. In classical complete transposition the venous connections to the heart are normal. Two parallel circuits exist and uncorrected transposition is incompatible with survival unless there are additional lesions which ensure adequate mixing of oxygenated and deoxygenated blood. The most common of these is a large ventricular septal defect with or without pulmonary stenosis. Initial survival depends on mixing of venous and arterial blood via a natural shunt or an artificial balloon atrial septostomy.

### *Senning and Mustard procedures*

Surgical management of this condition until the 1980s was by means of an atrial switch procedure (Mustard or Senning procedures) in which venous return to the heart is redirected at the atrial level to direct pulmonary blood flow to the right or systemic ventricle and systemic blood flow to the left or pulmonary ventricle.[85 110] The interatrial septum is removed and an intra-atrial baffle created which directs blood from the pulmonary veins across the atrial septal defect to the morphological right ventricle and the systemic arterial circulation. In the Senning procedure the baffle is constructed from native atrial wall while the Mustard operation involves the use of pericardium or foreign material such as Dacron to construct the intra-atrial baffle. Systemic venous blood is directed to the morphological left ventricle and into the pulmonary artery. These procedures are associated with a high incidence of potentially malignant arrhythmias (30–100%), baffle obstruction (10–15%) resulting in systemic venous congestion and pulmonary oedema, and right (systemic) ventricular failure as a consequence of a morphological right ventricle being required to support the systemic circulation.

Long-term follow-up at 16 yr of patients undergoing the Mustard procedure showed a survival of 91% for simple transposition and 60% for complex transposition, respectively. Survival at 16 yr was 78% in both groups for the Senning procedure. Good functional status or lack of symptoms are poor indicators of late outcome after these procedures and close follow-up is required to detect and treat late complications, including right (systemic) ventricular failure, arrhythmias and obstruction to venous return. The Mustard procedure is associated with a higher incidence of late arrhythmias than the Senning procedure.[55] These arise as a consequence of damage to the sinoatrial node or its blood supply, interruption of intra-atrial conduction pathways or damage to the atrioventricular node during an extensive atrial surgical procedure.[49,50] A cohort of 372 survivors of the Mustard procedure had mean resting heart rates that were consistently lower than age-matched controls and a decreasing percentage of subjects in sinus rhythm with time (57% by the end of the eighth post-operative year).[42] In combined surface ECG recording, exercise ECG, Holter monitoring and invasive electrophysiological studies in 87 patients after the Mustard procedure, there was sinus node dysfunction in 47% of patients, ventricular and supraventricular ectopy in 34% and atrioventricular block in 23% although symptoms of conduction disturbances were rare.[10] The commonest disturbance is a nodal rhythm or sinus bradycardia with recurrent episodes of atrial flutter. Supraventricular tachycardia and atrial fibrillation may also occur. There is a high incidence of potentially fatal arrhythmias in survivors of the Mustard procedure during exercise, even in patients without resting symptoms or arrhythmias.[79] Sudden death is common after both procedures and occurs in 5–8% of patients in some series[42] and tachyarrhythmias increase the risk of this event.[47,126] There is failure to increase the ejection fraction of the right (systemic) ventricle during exercise in more than 50% of asymptomatic patients 5–15 yr after the Mustard procedure and this is presumably also the case during the stresses which may be associated with trauma, anaesthesia and surgery. The presence of complex ventricular arrhythmias was the first predictor of failure of the ejection fraction to increase with exercise.[84] Tachyarrhythmias may cause impairment of ventricular function with exercise in those patients in whom the right (systemic) ventricle is not able to increase stroke volume and cardiac output. Inadequate cardiac output during exercise may then result in sudden death.

Obstruction to venous inflow to both atria has been reported after both procedures[42,47,116] but appears to be more common after the Mustard procedure. Depressed right (systemic) ventricular function has been observed in 50% of survivors at late follow-up[52,55] and it appears that systemic ventricular function declines with time in these patients. Subjects reached 80% of predicted maximum exercise tolerance. Factors contributing to this failure are systemic levels of preload and afterload, tricuspid regurgitation and atrial dysfunction secondary to surgery which is more common after the Mustard procedure.[55,127] Diagnosis and appropriate treatment of diminished right (systemic) ventricular function and baffle-associated problems are important in patients who have undergone these procedures.

### *Arterial switch procedure*

The arterial switch operation[61] in which the aorta is connected to the left ventricular outflow tract and the pulmonary artery to the right ventricular outflow tract has now largely replaced the atrial switch in appropriate patients. This procedure requires re-implantation of the coronary arteries from the pulmonary artery to the root of the aorta and leaves the pulmonary valve as the valve for the systemic circulation. It has clear advantages in that normal physiology is restored and atrial surgery other than closure of an atrial septal defect or septostomy is avoided. Short- and medium-term results are good and there is a low incidence of significant rhythm disturbances, although there is a 20–30% incidence of supraventricular and ventricular ectopics.[97] The long-term effects of supravalvular stenosis of the great arteries, obstruction at the level of the re-implanted coronary arteries and the function of the pulmonary valve in the systemic circulation are unknown.

At 10-yr follow-up of a cohort of 444 subjects who had undergone the arterial switch operation, left ventricular size, left ventricular mass, cardiac index, filling pressures, functional status and contractility were normal, with no evidence of time-related functional deterioration. There was a 30% incidence of regurgitation through the neo-aortic valve.[26] Other series have reported normal left ventricular mass,[41] left ventricular volume, ejection fraction and stress velocity index[14,41,88,128] after the arterial switch procedure. Neo-aortic regurgitation is usually mild but more severe in the presence of previous pulmonary artery banding. Causes include intolerance of systemic pressures by the valve, damage to the valve mechanism by coronary artery re-implantation and the circumferential suture line and damage to the valve by a prior pulmonary band. Anaesthesia should maintain a mild tachycardia and encourage vasodilatation. A period of pulmonary artery banding before definitive surgery represents a higher risk of subsequent myocardial impairment with depressed contractility,[14] abnormal regional wall motion,[119] myocardial perfusion abnormalities,[118] reduced ejection fraction,[8] insufficiency of the neo-aortic valve[128] and increased left ventricular volumes.[73]

## COARCTATION OF THE AORTA

The area of coarctation is characteristically located immediately beyond the origin of the left subclavian artery, at or just distal to insertion of the ligamentum arteriosum. A coarctation may also take the form of a diffusely narrowed aortic segment that begins distal to the innominate artery and ends at a localized constriction just beyond the left subclavian artery. The basic anatomical abnormality in coarctation of the aorta is a localized deformity of the media manifested by an infolding that concentrically narrows the aortic lumen. There is a 20–40% incidence of bicuspid aortic valve associated with coarctation. In the absence of surgical correction, more than 90% of patients with coarctation die before 50 yr of age from cardiovascular and cerebrovascular disease.[119] The longest follow-up of survivors after operation shows a probability of survival of more than 70% at 40 yr after surgery.[17] Treatment is by surgical resection with either end-to-end anastomosis or widening of the coarctation with a flap of the proximal left subclavian artery.

In patients who have undergone surgical repair of coarctation there is a high incidence at follow-up of hypertension, premature coronary artery disease, re-coarctation and aortic valve disease. Despite the early success of coarctation repair there is an ongoing increased risk of premature death in these patients. The majority of the excess mortality is caused by ischaemic heart disease and stroke.

Hypertension occurs in 12–66% of patients after repair[25 93] and the incidence appears to increase with the duration of long-term follow-up.[93] The occurrence of hypertension is related partly to age at repair, with more late problems seen after repair in adolescents and adults than after repair in infants.[11 13 23 25 70] Operation between 2 and 9 yr of age on an isolated coarctation usually reduces the resting arterial pressure to normal.[70] Hypertension contributes to the excess of deaths in this group from cardiovascular disease and cerebrovascular accidents. This excess mortality is seen even in subjects with normal arterial pressure when measured intermittently at rest. The excess mortality in these patients may result from hypertension which occurs during normal activities and exercise and which has been demonstrated using ambulatory arterial pressure monitoring.[74 89] The whole of the aortic arch is abnormal in coarctation and this abnormality persists after repair. In patients who have undergone repair, microscopy of aortic arch tissue shows narrowing of the arch, increased collagen and decreased smooth muscle which lead to increased rigidity and decreased pharmacological responsiveness.[108] These structural anomalies of the aorta which persist after repair probably contribute to the post-repair hypertension seen in these patients.[89] Adaptations of the paediatric left ventricle to increased afterload caused by a coarctation include increased ventricular mass, enhanced systolic function and subnormal left ventricular wall stress.[36] These changes persist after repair even in subjects without persisting gradients or resting hypertension and abnormal left ventricular systolic and diastolic function and increased ventricular mass are found even in normotensive patients long after successful coarctation repair.[68 74 82 89] Increased ventricular mass may cause rhythm disturbances or an imbalance between myocardial oxygen supply and demand. These changes may be accelerated by normal aging.

However, repair at a young age is associated with a higher likelihood of re-coarctation[17 34 107] which ranges in incidence from 8 to 44%. Young age at repair (less than 2 yr) and low weight are independent risk factors for re-coarctation. Re-coarctation occurs in up to 40% of survivors at 16 yr[67] and an increasing incidence of this complication is expected during long- term follow-up. This complication is related to incomplete resection of the lesion (residual coarctation), failure of growth at the anastomotic site (recurrent coarctation) or to a combination of the two. The technique of surgical repair is likely to influence the occurrence of re-coarctation as a consequence of incomplete resection of ductal tissue,[130] inadequate growth of the anastomosis, fibrosis and thrombosis. The technique of subclavian flap aortoplasty is considered to be associated with lower rates of re-coarctation than resection and end-to-end anastomosis[11 107] because it avoids the need for a circumferential aortic anastomosis which fails to grow adequately. The sacrifice of the left subclavian artery which this technique entails results in diminished pulses, minimal shortening and often claudication during exercise in the left arm.[114]

Significant aortic valve disease (pressure gradient or valvular insufficiency) occurred in 37% of subjects repaired in childhood and in 58% repaired as adults[11] and results in requirement for aortic valve replacement in a significant fraction of these survivors. In several series patients have died from aortic valve disease or from the complications of aortic valve replacement. Long-term follow-up over 25–44 yr of patients who underwent coarctation repair shows that age at operation of 1–2 yr is associated with the best balance of risk for re-coarctation (less than 3%), hypertension and premature death.[17]

### CAVO–PULMONARY ANASTOMOSES

The conditions of tricuspid atresia or univentricular double inlet ventricle are characterized by the absence or hypoplasia of one of the ventricular chambers which makes an anatomical biventricular repair impossible. The disadvantages of the series circulation which these conditions produce are poor oxygenation and impaired myocardial function because of the obligatory diastolic volume load which is borne by a ventricle which is simultaneously supplying both the systemic and pulmonary circulations. A univentricular circulation is inherently inefficient because of recirculation of systemic and pulmonary venous return. As a consequence of the decrease in pulmonary resistance with time, the proportion of the entire cardiac output passing through the lungs is likely to increase and present an increasing volume load to the ventricle with no increase in systemic oxygen delivery and a decline in myocardial function. The ventricle is then situated on an unfavourable part of the Frank–Starling curve and there is progressive ventricular dysfunction. Hypoxaemia, polycythaemia and increased blood viscosity also occur.

These patients usually undergo procedures which direct systemic venous blood to the pulmonary circulation without passage through a right ventricle. The surgical options for doing this are a superior vena cava–pulmonary artery anastomosis (Glenn-type procedure), a right atrium–pulmonary artery anastomosis (Fontan procedure) or a total pulmonary–caval connection. These various procedures separate the pulmonary and systemic circulations, eliminate pulmonary recirculation and direct systemic venous return to the pulmonary artery ensuring that only systemic venous blood passes through the lungs. In these arrangements flow of blood from the systemic venous system to the left atrium occurs entirely as a result of the pressure gradient between the vena cavae and the left atrium.

For this to succeed there must be a normal or low pulmonary vascular resistance and completely normal left ventricular filling pressures at rest and during exercise. Criteria for success include a low pulmonary vascular resistance and low pulmonary artery and left atrial pressures. In patients who meet these criteria the early mortality from the procedure should be less than 5%.

### *Glenn shunt*

The original cavo–pulmonary shunt was the Glenn shunt which involved anastomosis of the superior vena cava to the right pulmonary artery and provided perfusion of only the right lung. This has been largely superceded by the bi-directional Glenn shunt in which the superior vena cava is anastomosed to the main pulmonary artery to allow perfusion of both lungs. These procedures divert only superior vena caval blood to the pulmonary circulation and inferior vena cava blood continues to shunt from right to left within the heart and to contribute to subsequent hypoxaemia and significant limitation of exercise capacity. These operations are most often used as a staging procedure to a complete Fontan procedure but may be the definitive operation in children with anatomy which is unfavourable for a Fontan procedure.

The Glenn-type procedures are associated with persisting moderate hypoxaemia because of the persistent right-to-left shunting of inferior vena cava blood. The degree of palliation provided by these shunts is generally seen to diminish after 5–15 yr resulting in progressive hypoxaemia[33 71 72 90] with increasing numbers (over 40%) of patients requiring further palliation such as a definitive Fontan procedure or construction of a peripheral arteriovenous fistula. This is one of the reasons why a definitive Fontan procedure is now performed whenever possible. Reasons for this deterioration include decreased flow to the contralateral lung in the classical Glenn shunt and the development of significant superior vena cava–inferior vena cava communications. This may be a result of progressive development of systemic venous collateral vessels which decompress the superior vena cava system into the inferior vena cava system. These vessels can often be obliterated successfully by coil embolization. Pulmonary arteriovenous shunts also develop in 10% of patients[71] and these are not always amenable to embolization. The prevalence of these shunts appears to increase with time and the reason for their formation is unclear but may be caused by increased perfusion and pressure in the lower lung fields where these fistulae occur.[24 72] There is progressive hypoxia in these patients with its attendant problems of reduced exercise tolerance, polycythaemia and thrombosis.

### *Fontan circulation*

The original Fontan procedure involved anastomosis of the right atrium to the pulmonary artery with interposition of a homograft valve.[44] This was later modified so that the right atrium and pulmonary artery were connected by direct anastomosis of the right atrial appendage to the main pulmonary artery so avoiding the use of prosthetic material. Blood from the inferior vena cava is also directed to the pulmonary circulation after this procedure.

In appropriate patients the short- and medium-term results of these procedures are good. A complete Fontan procedure often results in an arterial oxygen saturation of approximately 95%. The price paid for this is high central venous pressures and high venous pressures in the hepatic, mesenteric and renal vascular beds. Late problems with the Fontan procedure largely result from chronic increases in right atrial, central venous and abdominal venous pressures. Peripheral oedema is common and may require diuretics to limit it. There is an increasing risk of death[45] after this procedure with a 10-yr survival in large series of 60%. Problems include a 15% incidence of protein-losing enteropathy and hypoproteinaemia at 10 yr, hepatomegaly, ascites and cirrhosis.[38] Pulmonary arteriovenous fistulae may also develop after the Fontan procedure in the same way as after the Glenn procedure.[24] Longer follow-up is necessary to determine if this becomes a common complication of the Fontan procedure. Supraventricular tachycardias have been reported with a 20-40% incidence between 5 and 15 yr after operation[38] and more than 40% of patients have rhythm abnormalities on 24-h ambulatory ECG at 10 yr,[29 121] including abnormal sinus node function, prolonged refractory condition of the atrium, delayed intra-atrial conduction, inducible atrial arrhythmias and the bradycardia– tachycardia syndrome. The risk of arrhythmias increases with the duration of follow-up, and life-long surveillance for these patients is required to determine the need for pharmacological therapy or pacemaker insertion. These patients have limited ability to increase cardiac output during exercise or stress. Cardiac index at rest and during exercise is low compared with controls and exercise may produce functional conduit obstruction in asymptomatic subjects.[48 86 104 105] Ventilation–perfusion abnormalities are common.

Other significant problems include thrombosis[35] and stroke.[38] Factors which may predispose to thrombus formation include low cardiac output (particularly if there are areas within the heart prone to stasis such as the pulmonary artery stump or an enlarged redundant right atrium), supraventricular arrhythmias such as atrial flutter and fibrillation, the use of synthetic material or anastomotic stenosis. There are abnormalities of the haemostatic mechanism predisposing to thrombosis in more than 60% of patients who have undergone a Fontan procedure.[28] The commonest of these is protein C deficiency. A review of cerebrovascular accidents after the Fontan procedure found a 2.6% incidence of stroke among 645 patients. Seven of sixteen patients were found to have intracardiac thrombus which in every case was in a position to generate systemic emboli.[39] Currently there are no well founded guidelines on the place of routine anticoagulation in these patients. Some institutions anticoagulate patients perceived as being at high risk of thrombotic complications.

The morbidity and mortality of a Fontan procedure in patients with a single ventricle may be reduced if staged procedures are performed with an intermediate stage of a bidirectional Glenn shunt being included. Each stage, however, exposes the sinoatrial node to the risk of injury and there is an increased incidence of sinoatrial node dysfunction in patients who have undergone staged procedures (16%) rather than a single Fontan procedure (8%).[78]

### *Total cavo–pulmonary connection*

A total cavo–pulmonary connection involves anastomosis of the superior vena cava directly to the right pulmonary artery and the construction of an intra-atrial conduit to direct inferior vena cava blood to the main pulmonary artery.[31] This innovation was introduced after the demonstration that the right atrium made an insignificant contribution by pumping to venous return in a valveless Fontan atriopulmonary connection and that inclusion of the whole right atrium in this circulation may be detrimental. The procedure was intended to reduce the amount of right atrial dissection required and consequent damage to the sinoatrial node, reduce volume distension of the right atrium, reduce turbulence in venous blood flow, possibly reduce the incidence of postoperative arrhythmias and reduce the incidence of right atrial thrombosis.

After these various procedures success depends on maintaining low values for pulmonary vascular resistance and left atrial pressure. Left atrial pressure reflects the diastolic properties of the ventricle and the function of the systemic atrioventricular valve. Factors which impede pulmonary blood flow include increased left ventricular end-diastolic pressure, atrioventricular valve stenosis or regurgitation, loss of sinus rhythm with cannon waves which increase left atrial pressure, pulmonary vein stenosis, increased pulmonary microvascular resistance, obstructed or stenotic pulmonary arteries or cavo–pulmonary anastomotic narrowing. These patients are very sensitive to changes in pulmonary vascular resistance and have a very limited ability to compensate for changes in this. After a cavo–pulmonary anastomosis an increase in pulmonary vascular resistance is manifested as a decrease in cardiac output and peripheral perfusion because of limited return to the systemic ventricle. Factors which may cause or contribute to an increase in pulmonary vascular resistance include hypoxaemia, hypercapnia, acidosis, excessive airway pressure, positive end-expiratory pressure and extrinsic pulmonary compression by pneumothorax or effusion. Central venous pressure must be maintained and manoeuvres which increase intrathoracic pressure such as intermittent positive pressure ventilation and positive end-expiratory pressure should be used cautiously. Any reduction in myocardial performance or loss of sinus rhythm are likely to be poorly tolerated. These patients should be considered to be at high risk of thrombotic complications and some antithrombotic regimen must be considered in all patients undergoing anaesthesia and surgery.

### ATRIOVENTRICULAR SEPTAL DEFECT

Atrioventricular canal septal defects are of two types. The partial defect or ostium primum results from failure of the septum primum to fuse with the endocardial cushions. This is usually associated with a cleft in the anterior leaflet of the mitral valve. There is left-to-right shunting at the atrial level, some degree of mitral regurgitation, development of increasing degrees of atrioventricular block and a significant risk of endocarditis on the cleft mitral valve. This lesion is usually repaired in infancy which involves closure of the defect and repair of the mitral valve. Results are very good although long-term sequelae may include residual pulmonary hypertension, persistent mitral regurgitation and atrioventricular block.

Complete atrioventricular septal defect results from failure of fusion of the septum primum with the endocardial cushions, failure of the endocardial cushions to fuse and a deficiency in the membranous portion of the ventricular septum. There is a common single atrioventricular valve rather than discrete tricuspid and mitral valves. This lesion usually results in what is effectively a univentricular heart. There is systemic pressure in both ventricles and early onset of pulmonary hypertension and heart failure. There is also the development of progressive degrees of atrioventricular conduction block and a high risk of endocarditis on the valve. Survival beyond childhood is unusual without corrective surgery unless there is pulmonary stenosis which protects the pulmonary circulation. Significant pulmonary vascular changes develop early in life but are said to be reversible if definitive surgery is carried out before 2 yr of age. Traditional management has consisted of a pulmonary artery band in the neonatal period to protect the pulmonary circulation from systemic pressures and high flows and definitive repair 2–3 yr later. In recent years definitive repair has been performed in the first year of life to minimize the long-term sequelae of a large left-to-right shunt and mitral regurgitation. Definitive surgery involves repair of the atrial and septal defects with patches of Goretex or Dacron and repair and resuspension of the left atrioventricular valve to restore competence. Surgical closure is associated with a risk of damage to the atrioventricular node and the bundle of His. In the early postoperative period transient complete atrioventricular block is common. Atrioventricular conduction block persists in 5% of patients and may appear late after repair in 2%. If the left atrioventricular valve is unrepairable a prosthesis is required. Atrial flutter or fibrillation occurs late in 5–10% of patients.

Long-term effects depend on residual conduction block, the degree of pre-existing pulmonary vascular disease and pulmonary hypertension, and left ventricular function. A common problem after repair is progressive left atrioventricular valve regurgitation which generally occurs because of separation of the two repaired components of the reconstructed septal leaflet of the valve. Subaortic stenosis may develop late after repair because of turbulence produced by the abnormal attachment of the left atrioventricular valve resulting in the formation of a discrete fibrous shelf which may need to be excised.

## RIGHT VENTRICLE–PULMONARY ARTERY CONDUITS

In the case of a lesion involving irreparable right ventricular outflow tract obstruction, an initial shunt procedure is performed to ensure pulmonary perfusion and subsequently followed by placement of an extracardiac valved conduit from the right ventricle to the pulmonary circulation to bypass the obstruction.[40 101] Relevant lesions include the tetralogy of Fallot with pulmonary atresia, truncus arteriosus and pulmonary atresia. Conduits used have included synthetic woven Dacron tubular conduits containing porcine aortic valves, valved aortic homografts and valved pulmonary homografts.

The commonest complication is obstruction which can result from stenosis at the distal anastomosis with the pulmonary vascular tree, compression of the ventricular end of the conduit during systole, accumulation of thrombotic and fibrous material on the wall of the conduit, compression of the conduit by the sternum and calcific or thrombotic stenosis of the valve. Other complications include regurgitation through an incompetent valve with an increased volume load and the possibility of high output heart failure. A loud murmur is almost universal from the conduit and should not be taken as evidence of stenosis or regurgitation. A feature of these conduits is that remarkably high gradients may exist across them in the absence of symptoms, and serial cardiac catheterization has been advocated as a method of surveillance.[3] Common symptoms of conduit failure include limitation of exercise tolerance, fatigue, dyspnoea and dizziness. Signs include increasing intensity of murmurs, heart failure and cyanosis.

The early use of porcine-valved Dacron conduits was associated with a high incidence of operative complications and early conduit failure resulting from graft rigidity or large size relative to the recipient. Late failures were caused by valve degeneration resulting in valvular stenosis and incompetence. Mechanisms of conduit failure as a result of valvular stenosis include thrombosis, commissural fusion and calcification. Valvular incompetence is caused by tears, fusion of cusps to the conduit wall and endocarditis. A particular problem is the accumulation of a pseudo-epithelium or peel which does not adhere to the tightly woven artificial material and lifts away to obstruct the conduit.[3] There is a high reoperation rate which was as high as 100% in one series.[63] With the growth of organ transplantation and expertise in harvesting organs and tissue preservation, human aortic and pulmonary homografts became available and artificial conduits were abandoned in favour of these natural conduits.

Initially, valved aortic allografts were used which have a lower early failure rate than artificial conduits but are also associated with operative complications, severe early calcification, late conduit obstruction[9 76 81] and valvular stenosis or regurgitation (60% at a mean follow-up of 3.4 yr).[5] Cryopreserved pulmonary allografts have several features which make them superior to aortic homografts for right ventricular outflow tract reconstruction. They are bifurcated and can be incorporated into repair of pulmonary artery stenoses. They also have a tissue consistency similar to that of the recipient pulmonary arteries. Anticoagulation is not necessary and they have better valvular mechanics than aortic allografts.[5] Pulmonary artery homografts have been shown to be more durable and to calcify to a lesser extent than aortic homografts.[9] Pulmonary artery homografts are now the conduit of choice for reconstruction of the right ventricular outflow tract.

## PREGNANCY

Increasing numbers of women with treated congenital heart disease are reaching reproductive age and anaesthetic management during labour and delivery is needed. Ideally there should be an opportunity for anaesthetic assessment of the patient early in pregnancy in the light of a recent cardiological review and regular assessments during pregnancy to avoid the potential situation of being confronted at short notice with a complex, high-risk parturient in labour. Management is based on knowledge of the normal physiological changes which occur during pregnancy, existing degree of cardiovascular impairment, associated pathophysiology and anticipated effects of analgesic and anaesthetic techniques. Features of interest are the existing anatomy, presence and magnitude of intracardiac shunts, degree of functional impairment, ability to exercise, ventricular failure, hypoxaemia and arrhythmias. The presence and severity of pulmonary hypertension is particularly important as the risk of maternal mortality approaches 30% with each pregnancy if there is significant pulmonary vascular disease.[92] Functional deterioration during pregnancy is likely in more than 50% of women with cyanotic heart disease compared with 15% of those with acyanotic disease.[111] Functional deterioration is also more likely in the presence of congestive cardiac failure than in its absence (30% *vs* 5%). Maternal congenital heart disease which results in residual hypoxaemia is associated with poor fetal growth, a high rate of spontaneous abortion, premature labour and a significant incidence of fetal complications. The risk to the fetus is broadly in proportion to the degree of maternal hypoxaemia with a 50% risk of fetal death if the maternal arterial oxygen saturation is less than 85% or the packed cell volume is more than 65%.[94] Neonates tend to be smaller than average with a high perinatal mortality. There is also the risk of congenital heart disease in the fetus as, although most patients do not have a recognizable genetic condition, there is a genetic component to the development of much congenital heart disease. The recurrence risk of congenital heart disease in a sibling of an index case is 1–8%.[7] As more women survive pregnancy accumulating data suggest that the risk in the offspring of an index case is higher, especially if the mother rather than the father is affected.[125]

Women with a surgically closed atrial septal defect, ventricular septal defect or patent ductus arteriosus without residual pulmonary hypertension and who are asymptomatic can expect to labour in an essentially normal manner,[111] as may patients with corrected tetralogy of Fallot without residual pulmonary stenosis or arrhythmias.[112] The haemodynamic stress imposed by pregnancy tends to be tolerated badly in the presence of stenotic lesions and low or fixed cardiac output states including the Fontan circulation. Failure of a morphological right ventricle acting as a systemic ventricle such as after the Mustard or Senning procedures for transposition of the great arteries may be seen.[77] In the presence of good myocardial function or regurgitant lesions, pregnancy is generally better tolerated.

In high-risk parturients, the objectives during analgesia and anaesthesia, if required, should be to preserve ventricular function, maintain adequate preload, avoid anaesthetic-induced myocardial depression and to prevent undesirable changes in the direction or magnitude of intracardiac shunts. In general vaginal delivery is the aim with Caesarean section reserved for obstetric indications. If fluctuations in arterial pressure and cardiac output associated with labour are particularly undesirable and may not be controlled, Caesarean section is indicated. Although in many high-risk patients there are theoretical reasons to avoid decreases in systemic vascular resistance or preload, especially if there is a right-to-left shunt in the presence of pulmonary hypertension (where increases in the shunt worsen hypoxaemia) or ventricular hypertrophy, extradural analgesia has been used in many such patients. When extradural block is produced slowly and incrementally with appropriate fluid loading and vasopressor use, hypotension can be minimized while the excellent analgesia it provides minimizes rapid fluctuations in preload, cardiac output and heart rate.[43 62 77 109] Voluntary pushing during the second stage of labour is minimized to avoid excessive Valsalva effects and delivery may be facilitated by forceps. Extradural or subarachnoid opioids have been used successfully to provide analgesia in high-risk cases.[2 4] This technique reduces the requirement for local anaesthetic administration and minimizes disturbances in maternal haemodynamics associated with vasodilatation and the reduction in preload, although the use of opioids alone is inadequate for operative delivery. Defective haemostasis is associated with anticoagulation, pulmonary hypertension and polycythaemia and should be considered before central regional blocks are performed. When general anaesthesia is used in high-risk patients the technique should be modified to avoid the risk of hypotension associated with a traditional rapid sequence induction.

## Conclusion

As the care of children with congenital heart disease continues to evolve, the spectrum of late complications associated with treatment is likely to change. The trend of performing early and definitive surgery whenever possible should improve the prognosis of several conditions and reduce the incidence of late complications. Newer techniques such as the arterial switch for transposition are expected to largely eliminate the late complications of atrial switch procedures. The use of cardiac catheterization techniques to close atrial septal defects and patent ductus arteriosus reduces the early morbidity and may further improve the good long-term outcome of these conditions.

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SHORT COMMUNICATIONS

# Wound infiltration with local anaesthetic after abdominal hysterectomy

T. F. COBBY AND M. F. REID

**Summary**

The study was performed to investigate if wound infiltration with 20 ml of 0.5% bupivacaine after abdominal hysterectomy improved analgesia and reduced morphine requirements from a patient-controlled analgesia system during the first 6 h after operation. Forty patients undergoing abdominal hysterectomy were allocated randomly to one of two groups. The study was performed in a double-blind controlled manner. Morphine requirements in the first 6 h after operation were similar in both the control (30.3 mg) and bupivacaine (29.0 mg) groups. Cumulative hourly morphine requirements did not differ significantly between the two groups. Pain scores assessed by visual analogue were similar in both groups. (*Br. J. Anaesth.* 1997; **78**: 431–432).

**Key words**

Pain, postoperative. Anaesthetics local, bupivacaine. Surgery, gynaecological

Beneficial effects of subcutaneous and intrafascial infiltration with local anaesthetic have been demonstrated for inguinal hernia repair and cholecystectomy, with reduced postoperative pain and opioid requirements.[1 2] However, little work has been performed on lower abdominal operations. A study of subcutaneous infiltration of local anaesthetic of the wound edges after lower segment Caesarean section demonstrated some reduction in morphine consumption but only on a weight-adjusted basis.[3]

The purpose of this study was to see if subcutaneous infiltration of bupivacaine after abdominal hysterectomy reduced morphine requirements after operation. Analgesia was assessed by pain scores, and opioid consumption was recorded using a patient-controlled analgesia (PCA ) system.

## Methods and results

After obtaining Ethics Committee approval, we studied 40 ASA I–II patients, aged 20–60 yr, weighing 40–100 kg; patients were undergoing elective abdominal hysterectomy and gave written informed consent to the study, which was performed in a prospective, double-blind, randomized manner.

Each patient was visited before operation and instructed on the use of the PCA machine. The use of a standard 100-mm visual analogue scale (VAS) for scoring pain was explained to the patient at this time. Patients were excluded if they had known allergy to bupivacaine, were concurrently using either opioids or non-steroidal anti-inflammatory drugs or were unable to use the PCA apparatus.

All patients received a standard anaesthetic. Anaesthesia was induced with fentanyl 3.0 $\mu$g kg$^{-1}$ and propofol 2–3 mg kg$^{-1}$. Atracurium 0.5 mg kg$^{-1}$ was administered to facilitate tracheal intubation and for neuromuscular block during the procedure. Anaesthesia was maintained with 1% isoflurane and 70% nitrous oxide in oxygen. Additional fentanyl and atracurium were used as required. Cyclizine 50 mg was given i.v. 20 min before the end of the operation as an antiemetic. Before antagonism of residual neuromuscular block with neostigmine 2.5 mg and glycopyrronium 0.5 mg, each patient was allocated randomly to one of two groups to receive either 20 ml of 0.5% bupivacaine by subcutaneous infiltration (to a maximum of 0.4 ml kg$^{-1}$) by the surgeon or no infiltration. In the recovery room, recovery staff administered i.v. morphine as postoperative analgesia as necessary, according to standard hospital procedures.

Patients then received additional analgesia by PCA with morphine 1 mg ml$^{-1}$, using a 1-ml bolus and a 5-min lockout, and additional antiemetic as required.

Pain was assessed hourly for the first 6 h after operation using a standard 100-mm VAS.

Differences in opioid requirements between the groups were assessed using an unpaired Student's $t$ test. Pain scores were compared using a Mann–Whitney $U$ test. $P<0.05$ was considered statistically significant.

Power analysis performed before the study indicated that 20 patients in each group would be required to detect a reduction in morphine use of 25% at 6 h, with a power of 0.8.

The groups were similar in characteristics. Mean doses of fentanyl given during operation were 234.7 (SD 67) $\mu$g and 240 (71.2) $\mu$g in the control and infiltration groups, respectively. Morphine requirements

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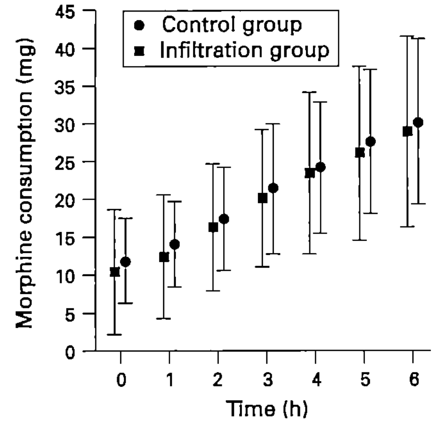

*Figure 1* Cumulative hourly morphine requirements (mean, SD) in the control and infiltration groups. The two groups have been separated for clarity.

were 11.8 (5.4) mg for the control group and 10.4 (8.2) mg for the infiltration group in the recovery area (time 0, fig. 1). At 6 h after operation, total morphine requirements were 30.3 (10.9) mg and 29.0 (12.5) mg, respectively. Similarly, cumulative hourly morphine requirements did not differ (Student unpaired *t* test) (fig. 1).

Pain scores on bending the knees and at rest during the first 6 h after operation were similar in both groups (Mann–Whitney *U* test).

## Comment

We have found that subcutaneous wound infiltration with 0.5% bupivacaine had no analgesic sparing effect after abdominal hysterectomy. Indeed, morphine consumption for the first 6 h was almost identical in the two groups (fig. 1). We may have failed to find a difference between the two groups because of the marked variability in individual opioid requirements. There was also a large variation in pain scores, despite the use of PCA. This, together with individual pharmacokinetic and pharmacodynamic handling of morphine, add to the variability in morphine consumption and may make it more difficult to demonstrate a morphine sparing effect of wound infiltration.

There were no differences in pain scores at rest or on movement. For a difference to be caused by wound infiltration with bupivacaine, a difference before 6 h would be expected. The 1-h pain scores in the control group were anomalous in that median pain scores were higher at rest than on movement, possibly because the women were still drowsy from their anaesthetic, but may indicate some unreliability of visual analogue pain scoring. However, Sinclair and colleagues[4] demonstrated a reduction in doses of i.m. buprenorphine and reduced mean visual analogue pain scores at rest in the first 24 h after application of lignocaine spray to the wound following closure of the muscular fascia after abdominal hysterectomy. They found the greatest improvement in pain scores in the first 6 h after operation.

Wound infiltration has been demonstrated to have an analgesic sparing effect after herniotomy[1] and provide similar analgesia to that of ilioinguinal nerve block for herniotomies in children.[5] There is conflicting evidence from previous studies as to the benefit of wound infiltration with local anaesthetics after intra-abdominal surgery. Trotter and colleagues[3] demonstrated no analgesic sparing effect after Caesarean section with wound infiltration. Other studies have found wound infiltration to be effective in reducing opioid demand and improving pain scores after Caesarean section and to be comparable with bilateral ilioinguinal nerve block.[6] These conflicting results may have been because the use of the term "wound infiltration" can encompass either subcutaneous or all layers of the incision. Studies have shown that by infiltrating all layers of the abdominal wall, opioid administration can be reduced after open cholecystectomy.[2]

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# Induction characteristics of 2% propofol in children

A. BORGEAT, T. FUCHS AND E. TASSONYI

## Summary

We have conducted a prospective, randomized study to evaluate the characteristics of induction of anaesthesia in children with 2% propofol. Children were allocated to receive propofol 3 mg $kg^{-1}$ (group A), 4 mg $kg^{-1}$ (group B) or 5 mg $kg^{-1}$ (group C) of the 2% formulation. We observed a high incidence of spontaneous movements (90%) in group A and an incidence of coughing of 70% in group C. Induction in group B was characterized by a short induction time, low incidence of spontaneous movements (20%), pain on injection (10%) and excellent conditions for manual ventilation. (*Br. J. Anaesth.* 1997; **78:** 433–435).

**Key words**
Anaesthetics i.v., propofol. Anaesthetic techniques, induction. Formulations, propofol. Children.

Propofol 1% is an i.v. anaesthetic agent which is now used routinely in paediatric anaesthesia.[1] Spontaneous movement is one of the side effects observed during induction of anaesthesia with 1% propofol.[2] It was demonstrated that increasing the loading dose from 3 to 5 mg $kg^{-1}$ resulted in a significant decrease in these movements.[2] However, the volume needed to be administered may be quite large and the required time to infuse such a volume through a 22-gauge or smaller catheter may be prolonged. It has been shown that slow injection is associated with more frequent and intense pain on injection,[3] an especially troublesome side effect in children.

A new formulation containing 2% propofol has been prepared recently; this reduces by half the volume and fat load. The 2% solution was prepared mainly for intensive care sedation, but the use of smaller volumes may be advantageous in children. We undertook this study to evaluate and assess the clinical tolerance and quality of induction of anaesthesia in children with this new formulation.

## Methods and results

After obtaining parental informed consent and institutional Ethics Committee approval, we studied 45 ASA I children, aged 5–12 yr. All children were undergoing elective ear, nose and throat (ENT) procedures of short duration. Exclusion criteria were known allergy to propofol or lignocaine, mental disorders or a previous problem with general anaesthesia.

EMLA emulsion cream (lignocaine 25 mg $g^{-1}$ and prilocaine 25 mg $g^{-1}$) was applied to the dorsum of both hands and covered with an impervious dressing approximately 1 h before operation. No sedatives were given before induction of anaesthesia. On arrival in the anaesthetic room, heart rate and arterial pressure were recorded with an automatic device (Cardiocap, Datex, Helsinki). Other monitors included a pulse oximeter (Cardiocap, Datex, Helsinki) and a precordial stethoscope. A 22-gauge catheter was inserted into a vein on the dorsum of the hand. Children were allocated prospectively to group A (2% propofol 5 mg $kg^{-1}$), group B (2% propofol 4 mg $kg^{-1}$) or group C (2% propofol 3 mg $kg^{-1}$) according to a computer randomized table. Propofol was premixed with lignocaine in a ratio of 10:1 (10 mg of propofol for 1 mg of lignocaine).

Children's lungs were preoxygenated for 1 min with oxygen ($F\text{I}_{\text{O}_2}$ 1.0). The induction bolus was given within 5–10 s. Two minutes later continuous infusion of propofol 0.2 mg $kg^{-1}$ $min^{-1}$ was started via an automatic pump (IVAC 711, San Diego, CA, USA). At this time children received alfentanil 20 mg $kg^{-1}$ and vecuronium 0.1 mg $kg^{-1}$.

A nurse was responsible for preparing and administering the propofol injection. At the end of the induction bolus, an independent investigator, unaware of the child's group assignment, observed and communicated with the child during induction and assessed the presence of pain on injection according to the following scale: (a) verbal complaints without withdrawal of the arm, (b) withdrawal of the arm with or without verbal complaints. The appearance of spontaneous movements was assessed according to the following classification: (a) movements of the hand and fingers, (b) movements of the arm, (c) movements of the arm and shoulder. Other variables assessed were induction time, defined as the time between end of propofol administration and loss of the eyelash reflex, arterial pressure and heart rate changes, erythema or cutaneous rash and cough/hiccup. Ease of ventilation of the lungs was assessed as excellent, smooth or unsatisfactory.

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*Table 1* Characteristics of induction with 2% propofol 4 mg kg$^{-1}$ (mean (SD or range) or number)

| Patient data | |
|---|---|
| *n* | 50 |
| Age (yr) | 8 (5–12) |
| Weight (kg) | 23 (8) |
| Sex (M/F) | 33/17 |
| Induction characteristics | |
| *n* | 50 |
| Induction time (s) | 12 (3) |
| Pain | |
| (a) | 5% |
| (b) | 5% |
| Spontaneous movements | |
| (a) | 15% |
| (b) | 5% |
| Erythema | 6% |
| Cough | 0% |
| Hiccup | 4% |
| Ease of ventilation | |
| 1 | 88% |
| 2 | 12% |
| 3 | 0% |

At the end of the study it was decided to add another 35 children to the group which showed the best clinical tolerance.

Patient characteristics were similar in the three groups. All groups were comparable in induction times, incidence of pain on injection and appearance of a rash or erythema.

A high incidence of spontaneous movements (90%) was observed in the 3-mg kg$^{-1}$ group which resulted in poor induction. In the 5-mg kg$^{-1}$ group, a high incidence of coughing (70%) was noted which rendered the management of ventilation unpleasant. In contrast, the 4-mg kg$^{-1}$ dose produced a rapid and smooth induction with few side effects (table 1).

Haemodynamic changes were comparable in all three groups, with a mean decrease in arterial pressure of 5–15% from basal values 1 min after injection, a decrease of 10–15%, 2 min and 15–20%, 3 min after administration of the propofol bolus. Changes in heart rate were also similar between groups, ranging from a mean decrease of 5% to an increase of 15%, 1, 2 and 3 min after induction.

## Comment

We have assessed the quality of induction of anaesthesia in children with the new formulation of 2% propofol and found that the induction dose of 3 mg kg$^{-1}$ was inadequate as we observed a high incidence of spontaneous movements. A dose of 5 mg kg$^{-1}$ was associated with a high incidence of coughing which interfered with manual ventilation. In contrast, a dose of 2% propofol 4 mg kg$^{-1}$ allowed rapid and smooth induction with few side effects. The ease of performing manual ventilation was particularly striking.

Induction time, that is interval between the end of drug administration and loss of the eyelash reflex, was 12 (3) s in the 4-mg kg$^{-1}$ group. Puttick and Rosen,[4] using the same criteria, found an induction time of 21 (3) s in children aged 2–11 yr who received 1% propofol 3.5 mg kg$^{-1}$. It is conceivable that a higher brain drug concentration is reached faster with the 2% formulation, thus explaining the very short induction time. A short induction time has advantages in young children, especially in those who have reduced pulmonary function.

One of the striking features of induction with 2% propofol 4 mg kg$^{-1}$ was the ease of performing manual ventilation. Manual ventilation was assessed as very easy and comfortable in 88% of children. Propofol 1% is also known to provide excellent intubating conditions; Pedersen[5] observed that sedation with 1% propofol in patients with hyperactive airway disease provided marked bronchodilatation.

Spontaneous movements limited to the finger and hand were observed in 15% of children and those involving the arm in 5%. The movements were, as described previously,[2] dystonic in nature. The incidence of spontaneous movements was similar to that reported by Purcell-Jones and colleagues[6] after a bolus of 1% propofol 2.5 mg kg$^{-1}$. The appearance of these movements decreased when the initial dose of 1% propofol was increased to 5 mg kg$^{-1}$,[2] but was also reported to be high when the induction dose was 3 mg kg$^{-1}$.[2] The trend in observing more severe and frequent spontaneous movements with a lower dose of 2% propofol is similar to that observed with 1% propofol.

Pain on injection was noted in 10% of children receiving 2% propofol pre-mixed with 1% lignocaine (in a ratio of 2% propofol 10 mg : lignocaine 1 mg). Pre-mixing 1% lignocaine with 1% propofol appeared to be the most efficient means of reducing pain on injection. The incidence observed in this study was similar to the results obtained with a mixture of 1% propofol–lignocaine.[7] The more concentrated formula of 2% propofol does not appear to increase the incidence of pain on injection when pre-mixed with lignocaine.

Other excitatory events such as cough and hiccup were rare in the 4-mg kg$^{-1}$ group. These results are comparable with those observed with 1% propofol.[2] We believe that the high incidence of cough observed with 2% propofol 5 mg kg$^{-1}$ may be explained by a sudden high propofol brain concentration leading to some excitatory effects on the cough centre.

Haemodynamic changes (arterial pressure and heart rate) did not differ from values observed after induction with the 1% formulation.

We have found that the new formulation of 2% propofol, at a dose of 4 mg kg$^{-1}$, provided induction characteristics in children similar to those observed with 1% propofol in terms of haemodynamic stability, pain on injection and spontaneous movements. However, the 2% formulation had the advantage of reducing the time of injection and volume of drug, of providing a short induction time and offering excellent conditions for manual ventilation.

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# A study of mixing conditions during nitric oxide administration using simultaneous fast response chemiluminescence and capnography

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## Summary

We have evaluated the mixing properties of nitric oxide in inspired gases for five different administration techniques. Nitric oxide and carbon dioxide were delivered to the ventilator system before the ventilator or after the ventilator as a continuous flow, either directly into the inspiratory limb or into a mixing chamber positioned in the inspiratory limb. Both gases were delivered as above but synchronized with inspiration. Mixing conditions were evaluated using fast response chemiluminescence for nitric oxide and capnography for carbon dioxide analysis. Administration of nitric oxide and carbon dioxide directly into the inspiratory limb as a continuous flow or with a magnetic valve-controlled synchronized flow resulted in peak concentrations of 236% and 220%, respectively, of expected values. The use of a mixing chamber reduced these values to 104% and 102%, respectively. Administration of nitric oxide as a continuous flow into the tubing of an intermittent flow ventilator resulted in highly fluctuating inspiratory peak concentrations, which could be avoided with a mixing chamber. (*Br. J. Anaesth.* 1997; **78**: 436–438).

**Key words**
Pharmacology, nitric oxide. Gases non-anaesthetic. Equipment, delivery systems.

Inhaled nitric oxide is used for the treatment of acute lung injury, persistent pulmonary hypertension of the newborn and right ventricular failure after cardiac surgery. Safe administration demands low levels of its toxic oxidation product, nitrogen dioxide. As the formation of nitrogen dioxide is proportional not only to the square of the nitric oxide concentration, but also to the contact time between nitric oxide and oxygen,[1] administration of nitric oxide after the ventilator has been advocated to reduce contact time and hence nitrogen dioxide formation.[2] To avoid highly fluctuating concentrations, delivery of nitric oxide into the inspiratory limb only during inspiration has been suggested. This study was designed to evaluate mixing properties of nitric oxide for five different delivery techniques.

## Methods and results

A Servo 900 C ventilator (Siemens Elema, Solna, Sweden) was driven with 100% oxygen via its low pressure inlet to generate a minute volume of 9.5 litre min$^{-1}$, at 10 and 20 cycles min$^{-1}$, with inspiratory times of 25% and 33%. Nitric oxide and carbon dioxide at flow rates of 250 ml min$^{-1}$ for each gas were delivered to the breathing system by two mass flow regulators (Bronkhorst Hightech BV, Ruurlo, The Netherlands), the flows of which were checked with a precision gas flowmeter (ADH 3000, J &W Scientific, Fisons, Folsom, CA, USA). The gases were added either before the ventilator or as a continuous flow immediately after the ventilator into the inspiratory limb, or into a mixing chamber and soda lime absorber connected in series with the inspiratory limb. They were also delivered as above, but synchronized with inspiration via a magnetic valve-controlled Siemens Servo 945 Nebulizer (Siemens Elema, Solna, Sweden).

The inspiratory limb was connected to an "alveolar lung chamber" (1 litre) in which a continuous flow of air 3.5 litre min$^{-1}$ was mixed to mimic lower "end-tidal" nitric oxide/carbon dioxide concentrations. The chamber was connected to an artificial lung with a compliance of 70 ml cm$^{-1}$ $H_2O$. At the Y-piece we attached a fast response chemiluminescence (CL) analyser for nitric oxide (NOX 4000, Seres, Aix en Provence, France) with a sampling rate of 1 litre min$^{-1}$, and capnography for carbon dioxide (Ultima SV, Datex, Helsinki, Finland) with a sampling rate of 250 ml min$^{-1}$. Nitric oxide and carbon dioxide tracings were recorded on a flat bed recorder. The mixing chamber–soda lime unit comprised two 900-ml canisters of which one was filled with 450 g of soda lime (Q-sorb, Anmedic AB, Vallentuna, Sweden), exhausted for carbon dioxide before the experiments. As the primary carbon dioxide concentration was 100% and the nitric oxide concentration was 1000 parts per million (ppm) in nitrogen (AGA Gas AB, Lidingö, Sweden), the expected concentrations at the Y-piece were 2.5 % for carbon dioxide and 25 ppm for nitric oxide, if complete mixing was achieved.

When carbon dioxide was administered before the

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*Table 1* Administration of carbon dioxide ($CO_2$) and nitric oxide (NO) before the ventilator (BV), as a continuous flow into plain tubing (C+PT), as a continuous flow into a mixing chamber (C+MC), synchronized with inspiration into plain tubing (S+PT) or synchronized with inspiration into a mixing chamber (S+MC). Ventilatory frequency (*f*) is 10 or 20 bpm and I: E ratio is 1:1 and 1:1.9. The "ideal" expected concentrations are 2.5% for $CO_2$ and 25 ppm for NO

| $CO_2$ concentration (%) | | | | | | | | | NO concentration (ppm) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *f* | I:E=1:1 | | | I:E=1:1.9 | | | | I:E=1:1 | | | I:E=1:1.9 | | | |
| | (bpm) | Max. | Min. | Mean | Max. | Min. | Mean | Morphology | Max. | Min. | Mean | Max. | Min. | Mean | Morphology |
| BV | 10 | N/A | N/A | 2.40 | N/A | N/A | 2.40 | Plateau | N/A | N/A | 24 | N/A | N/A | 24 | Flattened peak |
| | 20 | N/A | N/A | 2.35 | N/A | N/A | 2.35 | Plateau | N/A | N/A | 22 | N/A | N/A | 22 | Flattened peak |
| C+PT | 10 | 5.90 | 0.85 | N/A | 5.20 | 0.75 | N/A | Sharp peak | 42 | 15 | N/A | 33 | 16 | N/A | Sharp peak |
| | 20 | 4.00 | 1.00 | N/A | 4.00 | 1.00 | N/A | Sharp peak | 39 | 18 | N/A | 39 | 18 | N/A | Sharp peak |
| C+MC | 10 | N/A | N/A | 2.60 | N/A | N/A | 2.60 | Plateau | N/A | N/A | 28 | N/A | N/A | 27 | Flattened peak |
| | 20 | N/A | N/A | 2.40 | N/A | N/A | 2.40 | Plateau | N/A | N/A | 26 | N/A | N/A | 23 | Flattened peak |
| S+PT | 10 | 5.50 | 0.70 | N/A | 5.50 | 0.70 | N/A | Peak | 28 | 13 | N/A | 26 | 14 | N/A | Peak |
| | 20 | 3.20 | 1.20 | N/A | 2.80 | 1.40 | N/A | Peak | 26 | 17 | N/A | 24 | 18 | N/A | Peak |
| S+MC | 10 | N/A | N/A | 2.55 | N/A | N/A | 2.55 | Plateau | N/A | N/A | 23 | N/A | N/A | 22 | Flattened peak |
| | 20 | N/A | N/A | 2.40 | N/A | N/A | 2.40 | Plateau | N/A | N/A | 24 | N/A | N/A | 24 | Flattened peak |

ventilator or after the ventilator into the mixing chamber, whether as continuous or synchronized flow, final concentrations varied between 2.35% and 2.60%, with a clear plateau phase for each administration technique (table 1). For nitric oxide, this resulted in concentrations of 22–28 ppm, with only a flattened peak and no plateau phase. Continuous administration of both gases directly into the inspiratory tubing resulted in inspiratory carbon dioxide concentrations of 0.70–5.90% and nitric oxide concentrations of 15–42 ppm, both with a sharp peak at early inspiration. When administered synchronized with inspiration, concentrations varied between 0.70 and 5.50% for carbon dioxide and between 13 and 28 ppm for nitric oxide.

## Comment

Nitric oxide delivery systems should produce stable and uniformly distributed nitric oxide concentrations with minimal formation of nitrogen dioxide. A fixed inspired nitric oxide fraction can be obtained easily when nitric oxide is mixed with oxygen and air before the ventilator, using sophisticated and expensive devices such as mass flow regulators[3] or, alternatively, even simple flowmeters. This technique however is restricted to ventilators with a low pressure inlet. The gases can also be mixed at high pressure, which increases the number of usable ventilators. This technique necessitates the use of several blenders,[4] liable to oxidation by nitric oxide and nitrogen dioxide, requires rather complicated calculations when changes in nitric oxide and oxygen concentrations are necessary and may additionally increase nitrogen dioxide production as oxidation of nitric oxide is proportional to the cube of the gas pressure. Both techniques increase residence time of nitric oxide in the ventilator and are believed to enhance nitrogen dioxide formation.

Administration of nitric oxide in the inspiratory limb has been used to reduce the contact time between nitric oxide and oxygen.[2] Our experiments however showed that continuous administration of carbon dioxide and nitric oxide into the inspiratory limb of an intermittent flow ventilator resulted in fluctuating inspiratory concentrations at the Y-piece. For carbon dioxide, a peak of 236% and a minimum of 34% of the expected value was measured, whereas for nitric oxide values varied between 160 and 60%. This also shows that the fast response CL analyser cannot detect these rapid fluctuations and considerably underestimates peak and overestimates minimum concentrations. With a continuous flow, nitric oxide supplied from a concentrated cylinder (usually approximately 1000 ppm) accumulates at the entry point in the inspiratory limb during expiration and forms a nitric oxide plug. The latter moves nearly undiluted to the patient during the next inspiration. Although we have no flow data and consequently no idea of the volume of gas with the high concentration, we expect that the first part of the tidal volume would preferentially reach alveoli with a low time constant, exposing them and their bronchiolar structures to high nitric oxide concentrations. This may result not only in nitric oxide related toxicity, but also in inhomogeneous distribution of nitric oxide in the lungs. In view of our data, dose–response curves in studies where nitric oxide was delivered as a continuous flow into the inspiratory limb may have to be reconsidered, as it is not clear if nitric oxide is mixed completely with the tidal volume when entering the lungs. Furthermore, the equipment used to monitor nitric oxide and nitrogen dioxide concentrations was probably not sophisticated enough to detect these peak concentrations. Synchronizing nitric oxide flow with inspiration with a magnetic valve clearly does not solve the problem of inhomogeneous mixing. A pressure increase upstream of the synchronizing unit during expiration probably results in bolus injection as soon as it opens during inspiration, as suggested by carbon dioxide concentrations between 220 and 28% of expected values. Recently, methaemoglobin concentrations of 67% were reported in a patient receiving nitric oxide 8–45 ppm, as measured with a CL analyser.[5] Nitric oxide was delivered in the inspiratory limb with a flow synchronized to ventilator flow. Our data support the authors' speculation that the CL analyser underestimated real inspiratory peak concentrations. The latter were probably responsible for the extremely high methaemoglobin concentrations in this patient.

In our experiments a mixing chamber–soda lime canister provided effective mixing of the gases, as evidenced by a plateau phase in the carbon dioxide curves, but increased residence time of the gases in the system. Our data provide no conclusive information on nitrogen dioxide production for two reasons: soda lime was exhausted for carbon dioxide and may not have had its full capacity to scavenge nitrogen dioxide, and the CL analyser was not fast enough to detect rapid changes in nitric oxide concentrations and therefore was unable to measure corresponding nitrogen dioxide concentrations correctly, as the latter are measured indirectly via nitric oxide.[4] It might be interesting to evaluate our system with a smaller mixing chamber or with a single soda lime canister serving both as a mixing chamber and nitrogen dioxide scavenger.

A mixing chamber in the system does not necessarily increase nitrogen dioxide production dramatically, provided that adequate mixing is achieved. As nitric oxide oxidation is proportional not only to the contact time with oxygen, but also to the square of its own concentration, even a short peak in nitric oxide may result in considerable nitrogen dioxide production. Consequently, nitric oxide delivery systems using more sophisticated technology such as NODOMO (Drager, Germany), Pulmonox (Messer Griesheim, Austria), the new Ohmeda device (Ohmeda, USA) and the system described by Young,[6] may synchronize nitric oxide flow correctly and generate less nitrogen dioxide. However, these systems require expensive technology such as a mass flow controller and a pneumotachograph[6] or a very fast electronic mixer as in the NODOMO. The latter also has a humidifier in the system which acts as a mixing chamber. The Pulmonox and Ohmeda device measure inspiratory flow and deliver nitric oxide into the inspiratory limb proportional to the latter.

The performance of systems which deliver nitric oxide into the inspiratory limb depend on the accuracy of measuring the ventilator flow pattern (inspiratory time 0.75–1.5 s) and the delay in matching nitric oxide flow (5–20 ml per breath) with the latter. Impaired matching or any mechanical delay in nitric oxide delivery inevitably results in inhomogeneous distribution of concentrated nitric oxide in the inspiratory gases.

In summary, continuous administration of nitric oxide into the tubing of an intermittent flow ventilator resulted in a very fluctuating inspired nitric oxide fraction. Interposition of a mixing chamber may avoid this problem.

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# Effects of acute administration of morphine on right atrial catecholamine content and heart rate in chronically morphine-treated rats

J. V. RABADAN, M. V. MILANÉS AND M. L. LAORDEN

## Summary

The purpose of this study was to determine if chronic administration of the preferential μ agonist, morphine, induced changes in cardiac catecholamine content. In rats treated with morphine for 7 days, a challenge dose of morphine 30 mg $kg^{-1}$ i.p. increased atrial noradrenaline (mean 1123.8 (SEM 62.2) ng $g^{-1}$), adrenaline (79.48 (8.5) ng $g^{-1}$) and dopamine (46.0 (1.0) ng $g^{-1}$) content whereas dopamine turnover was decreased; this was accompanied by a decrease in the frequency of contraction of the isolated right atria. There were no changes in noradrenaline, adrenaline, dihydroxy phenylacetic acid (DOPAC) or DOPAC:dopamine ratio in placebo-treated rats. These results demonstrated that acute administration of morphine in morphine-treated rats produced inhibition of neuronal catecholamine activity in the heart which could be responsible for the decrease in atrial contraction frequency. (*Br. J. Anaesth.* 1997; **78**: 439–441).

**Key words**
Sympathetic nervous system, catecholamines. Cardiovascular system, effects. Analgesics opioid, morphine. Rat.

The cellular and molecular basis underlying tolerance to, and physical dependence on, opioids are still uncertain.[1] Thus an alternative mechanism has been sought to explain the development of opioid tolerance/dependence and effects on drug withdrawal, including adaptive changes in neurotransmitter systems that appear to be the target of opioids. Thus in naïve rats, the hypothalamic content of noradrenaline and dopamine was reduced after acute administration of morphine, which suggests that stimulation of opioid receptors produces an increase in the release of these amines in the hypothalamus.[2] In contrast, the morphine-induced reduction in hypothalamic noradrenaline and dopamine concentrations was inhibited in chronically morphine-treated rats, which suggests that tolerance is developed to the effect of the opioid on noradrenergic and dopaminergic neurones.[2] In addition, chronic administration of opioids has been shown to increase, in the locus coeruleus (LC), concentrations of cAMP-dependent protein kinase and substrates for protein kinase, including tyrosine hydroxylase,[3] the rate-limiting enzyme in the biosynthesis of catecholamines. Recent evidence indicates that many of these intracellular adaptations are caused by changes in levels of specific proteins and their mRNA, suggesting that regulation of gene expression, via second messengers, may contribute to tolerance, dependence and withdrawal in the LC.[3]

Although it is well known that catecholamines play a significant role in opioid tolerance and dependence in the central nervous system, little is known of the cardiovascular changes during morphine tolerance or dependence. Previous studies have indicated that catecholamines play an important role in the sympathetic manifestation of the abstinence response in morphine-dependent rats.[4 5]

As the processes involved in tolerance may include the central and peripheral nervous system, this study was undertaken to determine changes in content of noradrenaline, adrenaline, dopamine and its metabolite, dihydroxy phenylacetic acid (DOPAC), in the right atria during morphine tolerance. In addition, we determined if such changes correlated with alterations in atrial contraction frequency in the rat.

## Methods and results

Male Sprague–Dawley rats (200–250 g) were housed four to five per cage under a 12 h light–dark cycle (light 08:00–20.00) in a room with controlled temperature (22±1°C) and humidity (50±10%), and food and water available *ad libitum*. The studies reported in this article were carried out in accordance with the Declaration of Helsinki.

Morphine tolerance was induced by s.c. implantation, under light ether anaesthesia, of pellets containing morphine base (75 mg). The implantation schedule consisted of one pellet on day 0, two pellets on day 2 and three pellets on day 4. Control groups received placebo pellets (lactose) according to the same schedule. Animals were killed on day 7

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(08:30–09:00). With this dose schedule, morphine-treated rats show complete tolerance to the effects of morphine.[26] On day 7, rats were treated acutely with saline i.p. or morphine 30 mg $kg^{-1}$ i.p. and killed 30 min later.

There were four experimental groups: (1) chronic placebo–acute saline i.p.;

(2) chronic placebo–acute morphine i.p.; (3) chronic morphine–acute saline i.p.; and (4) chronic morphine–acute morphine i.p.

Noradrenaline, adrenaline, dopamine and DOPAC concentrations were estimated in the right atria of the rat by high pressure liquid chromatography with electrochemical detection (HPLC/ED, Waters Millipore, MA, USA). After decapitation, the chest was opened with a midsternal incision and the right atria were dissected and stored at −80°C until assayed for catecholamines. The right atria were weighed frozen and immediately placed in a dry ice-cooled polypropylene vial and homogenized with a Polytron homogenizer (setting 5 for 30 s) in 1 ml of perchloric acid 0.1 mol $litre^{-1}$ containing EDTA 2.7 mmol $litre^{-1}$ and 3,4 dihydroxy- benzylamine (DHBA 5 pg $\mu l^{-1}$; Waters, MA, USA) as internal standard. The homogenates were centrifuged (15000 rpm, 4°C, 15 min), the supernatant layer was removed into a 1-ml syringe and filtered through a 0.22-μm GV (Millipore), and 10 μl of each sample was injected into a 5 μm $C_{18}$ reverse-phase column (Waters). Electrochemical detection was accomplished with a glassy carbon electrode set at a potential of +0.65 V *vs* the silver–silver chloride reference electrode. The mobile phase consisted of a 95:5 (v/v) mixture of water and methanol with sodium acetate 50 mmol $litre^{-1}$, citric acid 20 mmol $litre^{-1}$, 1-octyl-sodium sulphonate (3.75 mM9, di-n-butylamine 1 mmol $litre^{-1}$) and EDTA 0.135 mmol $litre^{-1}$, adjusted to pH 4.3. Flow rate was 0.9 ml $min^{-1}$. Chromatographic data were analysed with a Waters 740 Date Module integrator and quantified using the peak area ratio of the internal standard. Atrial content of catecholamines was expressed as ng/g wet weight of tissue.

The right atria were isolated and suspended in a 10-ml organ bath. Tyrode solution of the following composition (mmol $litre^{-1}$) was used: NaCl 136.9; KCl 5.0; $MgCl_2$ 1.05; $CaCl_2$ 1.8; $NaH_2PO_4$ 0.4; $NaHCO_3$ 11.9; glucose 5.0. The bathing solution was maintained at 37°C, pH 7.4, and bubbled with 95% oxygen and 5% carbon dioxide. Each preparation was suspended under a resting tension of 0.5 g and equilibrated for 45 min before the start of the experiments. The right atria were beating spontaneously and the frequency of contraction was measured using a force-displacement transducer (Grass FT-03) and recorded on a Letica polygraph.

Concentration–response curves ($10^{-9}$–$10^{-2}$ mol $litre^{-1}$) to morphine were composed for the isolated right atria from chronically morphine-treated rats and from the respective controls chronically treated with lactose pellets.

Each drug concentration was added to the organ bath in a volume of 0.1 ml in a cumulative manner. Concentrations of drugs were increased after a steady-state response had been attained with the previous concentration or after 5 min in the absence of response.

Pellets of morphine base (Alcaliber Labs., Madrid, Spain) or lactose were prepared by the Department of Pharmacy, Clinic Hospital (Madrid, Spain). Morphine (Alcaliber Labs., Madrid, Spain) was prepared fresh every day, dissolved in sterile 0.9% NaCl (saline) or distilled water.

Data are expressed as mean (SEM). Statistical differences in the content of noradrenaline, adrenaline, dopamine, DOPAC and in the DOPAC:dopamine ratio were analysed by two-way analysis of variance followed by the Newman–Keuls *post hoc* test. The results obtained *in vitro* are expressed as a fraction of the change in the frequency of contraction produced by a maximum dose of morphine (mean (SEM) of *n* animals). In this case statistical analysis was performed by one-way analysis of variance followed by the Newman–Keuls *post hoc* test. Differences with a *P* value less than 0.05 were considered significant.

Acute administration of morphine to morphine-treated rats induced an increase ($P<0.01$; $P<0.001$) in atrial content of noradrenaline (1123.8 (62.2) ng $g^{-1}$), adrenaline (79.40 (8.5) ng $g^{-1}$) and dopamine (46.0 (1.0) ng $g^{-1}$), whereas dopamine turnover

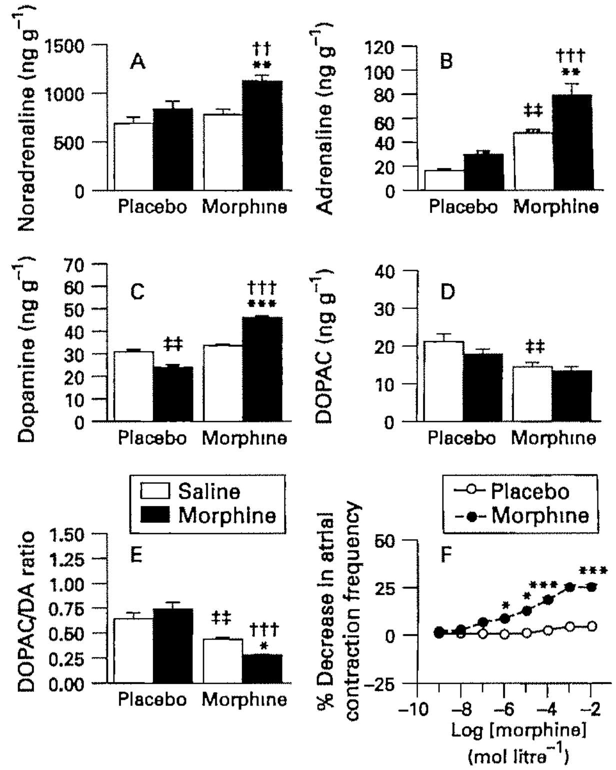

*Figure 1* Atrial noradrenaline (A), adrenaline (B) dopamine (C), DOPAC (D) concentrations and DOPAC/dopamine (DA) ratio (E) in placebo- and morphine-treated rats 30 min after acutely injected saline i.p or morphine 30 mg $kg^{-1}$ i.p. Each bar represents the mean (SEM) of 4–5 experiments. *$P<0.05$, **$P<0.01$, ***$P<0.001$ compared with morphine and saline; ††$P<0.01$; †††$P<0.001$ compared with placebo and morphine; ‡‡$P<0.01$ compared with placebo and saline. (F) Effects of morphine on atrial rate in the isolated right atria from morphine (control rate 250 (1.0) beat $min^{-1}$)- or placebo (control rate 252 (1.2) beat $min^{-1}$)- treated rats. Each point represents the mean (SEM) of five experiments for each experimental group. *$P<0.05$, ***$P<0.001$ compared with placebo.

(0.28 (0.01) ng $g^{-1}$) was decreased ($P<0.05$; $P<0.01$) compared with morphine-pretreated animals injected acutely with saline or placebo-treated rats given morphine. Administration of morphine to placebo-treated rats decreased ($P<0.01$) the content of dopamine (24.0 (1.7) ng $g^{-1}$) without significant changes in the concentrations of noradrenaline (844.20 (69.5) ng $g^{-1}$), adrenaline (29.6 (2.9) ng $g^{-1}$), DOPAC (17.66 (1.4) ng $g^{-1}$) or the DOPAC:dopamine ratio (0.74 (0.07) ng $g^{-1}$) compared with control groups given saline (fig. 1).

Concentration–response curves for morphine $10^{-9}$–$10^{-2}$ mol $\text{litre}^{-1}$ were obtained in placebo- or morphine-treated rats. In placebo-treated animals, morphine $10^{-9}$–$10^{-5}$ mol $\text{litre}^{-1}$ did not change atrial contraction frequency in the right atria. Higher concentration of morphine induced a small decrease (5 (0.5) %). However, in the morphine-treated rats, morphine induced a significant ($P<0.05$; $P<0.001$) decrease in atrial contraction frequency at concentrations of $10^{-6}$ –$10^{-2}$ mol $\text{litre}^{-1}$. The maximum effect was 25 (1.3) % (fig. 1).

## Comment

We conclude that acute administration of morphine in morphine-treated rats produced inhibition of neuronal catecholamine activity in the heart which could be responsible for the decrease in atrial contraction frequency.

## Acknowledgements

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CASE REPORTS

# Obstructive sleep apnoea syndrome: is this an overlooked cause of desaturation in the immediate postoperative period?

K. VIDHANI AND B. T. LANGHAM

## Summary

We report the case of a 38-yr-old man who presented for an emergency mastoidectomy and suffered from severe upper airways obstruction in the postoperative period. Subsequent questioning revealed a history of heroic snoring and further investigations proved a diagnosis of obstructive sleep apnoea. (*Br. J. Anaesth.* 1997; **78**: 442–443).

**Key words**
Ventilation, apnoea. Sleep apnoea. Airway, obstruction. Complications, obstructive sleep apnoea.

Patients with obstructive sleep apnoea are classically obese and complain of hypersomnolence and severe heroic snoring. Surgical treatment of these patients is becoming common place and their anaesthetic management is well defined. However, not all patients present a classical picture and we discuss a mode of presentation after anaesthesia in a previously undiagnosed patient.

## Case report

A 38-yr-old man presented for anaesthesia for an emergency mastoid operation. Preoperative assessment showed him to be 183 cm in height, weighing 96 kg and of muscular build (body mass index 28). He had undergone previous uneventful general anaesthesia with a Cormack and Lehane[1] view at laryngoscopy of grade 2, 4 yr previously. On examination of the oropharynx he had a Mallampati[2] score of 2, good mouth opening and normal dentition. His general health was good although he admitted to smoking 30 cigarettes per day and was receiving cimetidine for sporadic dyspepsia. All investigations were normal.

Standard monitoring was applied in the anaesthetic room and a vein cannulated. The patient's lungs were preoxygenated and rapid sequence induction with thiopentone 500 mg and suxamethonium 100 mg and cricoid pressure was carried out. Laryngoscopy proved difficult because of inability to lift the epiglottis from the posterior pharyngeal wall. Intubation was accomplished by passing the laryngoscope beyond the epiglottis as with a Magill blade. On return of neuromuscular function a dose of atracurium 50 mg was given and the patient's lungs were ventilated using a Nuffield Penlon ventilator via a Bains breathing system with 1–2% isoflurane and 70% nitrous oxide in oxygen. End-tidal carbon dioxide partial pressure was maintained at 4.5 kPa. Analgesia was provided by morphine 10 mg i.v., and droperidol 1 mg was given for postoperative nausea and vomiting. Arterial pressure was maintained at 100 mm Hg systolic at the request of the surgeon. At the end of the procedure residual neuromuscular block was antagonized with neostigmine 2.5 mg and glycopyrronium 0.5 mg was given. The patient was allowed to wake up and the trachea extubated on his side when it was judged that full neuromuscular function had returned.

On extubation he became agitated and had noisy breathing resembling severe snoring with flaring of the nostrils and associated desaturation. At this point we decided it was important to examine the upper airway to exclude obstruction. Anaesthesia was again induced using isoflurane in 100 % oxygen. On laryngoscopy there was no foreign body or swelling present in the upper airway and the epiglottis and larynx appeared normal. A nasal and oral airway were inserted and a normal respiratory pattern with good tidal volumes and an $Sp_{O_2}$ of 100% were obtained. The patient was allowed to wake up. However, when the patient was awake enough to spit out the airways he again developed severe upper airways obstruction and the trachea was reintubated rapidly using propofol 150 mg, suxamethonium 100 mg and atropine 0.6 mg. As there was found to be nothing obstructing the airway it was decided to allow the patient to wake up and self extubate in a sitting position. This was successfully achieved but the apparent upper airways obstruction recurred with a decrease in $Sp_{O_2}$. The MIE anaesthetic face mask was applied tightly to the patient's face with the Heidbrink valve partially closed. This manoeuvre improved the patient's condition and consequently he was admitted to the intensive care unit for oxygen therapy with +5 cm $H_2O$ of CPAP. He was also given dexamethasone 16 mg to reduce soft tissue swelling from repeated

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laryngoscopy. A lateral soft tissue neck x-ray showed no abnormality. Over the next 12 h the upper airway "snoring" subsided and the patient returned to the postoperative ward the following day.

On questioning the patient and his partner in the postoperative period a history of severe snoring became apparent, such that the sleep of the partner was seriously disturbed. There were no other features of obstructive sleep apnoea. Subsequently the patient was referred to the sleep studies laboratory. Overnight $Sp_{O_2}$ monitoring (the standard test carried out in this hospital for diagnosis of obstructive sleep apnoea) revealed periods of desaturation consistent with a diagnosis of mild obstructive sleep apnoea with a minimum $Sp_{O_2}$ of 78%, mean $Sp_{O_2}$ of 91% and an average of 31 dips $h^{-1}$. A trial of nasal CPAP+7.5 cm $H_2O$ achieved satisfactory oxygenation.

## Discussion

Obstructive sleep apnoea is a common but often undiagnosed condition that may affect 1% of the population.[3] The major problem is that of episodic hypopnoea or apnoea during sleep, the cause of which usually results from partial or complete obstruction of the upper airway. The clinical features include loud snoring (95%), day-time sleepiness (90%), unrefreshing and restless sleep (40%), morning headache, nocturnal choking, reduced libido, morning drunkenness, ankle swelling and enuresis. The syndrome occurs in all ages but is most common in late middle age, the male population and the obese, although it is well recognized that the patient need not be obese or somnolent to have significant sleep fragmentation or airway obstruction.

Problems may occur during induction of anaesthesia, in particular difficult intubation[4] and maintenance of the airway because of associated anatomical problems. Maintenance of anaesthesia requires controlled ventilation as spontaneous ventilation may lead to profound underventilation, acidosis, hypercapnia and hypoxia.[5] Before extubation patients should be awake and extubation should be in the sitting or lateral position. After operation, loss of the upper airway may still occur as oedema in this region may accumulate. Patients may benefit from nasal CPAP at this point and the majority of these patients with a known diagnosis of obstructive sleep apnoea should be managed in the intensive care unit or the high dependency unit for a variable period.

Our patient was seen in the preoperative period and presented no clinical features of obstructive sleep apnoea. He was of muscular build, did not appear obese and assessment of his airway revealed no abnormal features suggestive of a difficult intubation. He was anaesthetized 4 yr previously when intubation had been carried out successfully and anaesthesia had been uneventful. During our anaesthetic, intubation had proved more difficult with the laryngeal inlet being obscured by the epiglottis and requiring two attempts at intubation. Maintenance of anaesthesia was uneventful but extubation and the subsequent period proved difficult with upper airway obstruction. During this period we considered the likely causes of this problem to be: obstruction at the lips, obstruction by the tongue, obstruction above the glottis by a foreign body, saliva, vomitus, blood or oedema and obstruction at the glottis.[6] Repeat laryngoscopy excluded these causes and a clear airway was maintained while the patient was deeply anaesthetized with an airway *in situ*. The problem recurred when the airway was rejected by the patient. As we have stated the larynx was reintubated and then extubated with the patient fully awake in the sitting position and CPAP applied. At this point we considered a diagnosis of obstructive sleep apnoea and we feel that the initial difficulty with intubation had exacerbated his previously undiagnosed condition by causing minimal oedema of the upper airway, most likely the tongue. Subsequent investigation proved that this patient had obstructive sleep apnoea syndrome.

A diagnosis of obstructive sleep apnoea has often been made when these patients present for surgery, which may be of a corrective nature for their underlying diagnosis and as a consequence appropriate anaesthetic measures may be taken. Our patient was undiagnosed and appeared to have no features that would raise suspicion of obstructive sleep apnoea. However, on postoperative questioning he admitted to heroic snoring (a feature that occurs in 95% of cases), and had we obtained this history in our preoperative assessment our anaesthetic management would have been altered appropriately. This would have included minimizing the use of opioid analgesia (using NSAID and local anaesthetic infiltration), ensuring the patient was fully awake in the sitting position before extubation with a means of delivering CPAP if required and an appropriate safe environment for the patient in the postoperative period. We therefore agree with Dodds[5] that the question "Do you snore" should be asked in all preoperative assessments.

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# Intentional asystole during endoluminal thoracic aortic surgery without cardiopulmonary bypass

A. B. BAKER, M. J. BOOKALLIL AND G. LLOYD

## Summary

We describe in three patients the use of adenosine to arrest the heart without cardiopulmonary bypass during endoluminal repair of thoracic aortic aneurysms. The pharmacology of adenosine, a purine nucleoside present in all cells, is reviewed briefly, with special reference to its use in causing transient asystole, which is required for successful surgical expansion of the graft stent in the thoracic aorta. (*Br. J. Anaesth.* 1997; **78**: 444–448).

**Key words**
Pharmacology, adenosine. Surgery, vascular.

The advent of endoluminal grafting of the aorta[1] has required new approaches to the anaesthetic management of patients, particularly during balloon expansion of the aortic stent when arterial pressure must be reduced to prevent misplacement of the stent and damage to the proximal aorta or heart. We report three patients who received i.v. bolus doses of adenosine with the intention of causing asystole and hypotension at the time of expansion of the aortic stent of endoluminal grafts to the thoracic aorta.

Adenosine ("Adenocor" Sanofi Winthrop Pty Ltd), which is a relatively new antiarrhythmic agent for treating supraventricular tachycardia, is a naturally occurring purine nucleoside which transiently inhibits adenyl cyclase and 3, 5-cyclic adenosine monophosphate (cAMP) by binding to adenosine receptors, and has been shown to have major cardiovascular actions[2 3] (depression of sinoatrial (SA) and atrioventricular (AV) nodes; reduction in atrial contractility; attenuation of catecholamine effects primarily on the ventricles; depression of ventricular automaticity; and attenuation, via a presynaptic action, of adrenaline-induced noradrenaline release). The short duration of action, short half-life and effects on heart conduction make adenosine a useful drug in the diagnosis and management of supraventricular tachycardias such as Wolff–Parkinson–White syndrome.[4 5] Adenosine has also been useful in myocardial preservation during cardiac surgery because of cardiac arrest with a hyperpolarized myocardium rather than the more usual depolarized state,[6] although this has been challenged.[7]

## Case reports

### PATIENT NO. 1

A 38-yr-old female presented with an aneurysm of the thoracic aorta just distal to a previous coarctation which had been repaired at the age of 6 yr. Angiography showed normal coronary arteries and ventricular function. She was receiving ramipril 5 mg mane and oxazepam 15 mg mane. Preoperative creatinine concentration was 61 μmol $\text{litre}^{-1}$ (increasing to 69 μmol $\text{litre}^{-1}$ after operation), haemoglobin 129 g $\text{litre}^{-1}$ (decreasing to 87 g $\text{litre}^{-1}$, 3 days after operation even with transfusion during operation), and platelets $320 \times 10^9$ $\text{litre}^{-1}$ (decreasing to $188 \times 10^9$ $\text{litre}^{-1}$, 2 days after operation). After premedication with papaveretum 15 mg and hyoscine 0.3 mg, anaesthesia consisted of tracheal intubation using thiopentone and tubocurarine block, and isoflurane and nitrous oxide in oxygen. Intra-arterial, pulmonary arterial, capillary wedge and central venous pressures were measured.

Surgical access was via surgical exposure of the left common iliac artery, and percutaneous cannulation of the right brachial artery. Adenosine was used at the time of balloon inflation to expand the stents in the descending thoracic aorta. Two grafts (White-Yu GAD 22 mm×7 mm) were used, one inside the distal part of the other (the so-called trombone technique).[8] With the patient heparinized, receiving 100% oxygen, and after a trial dose (of 12 mg) administered via the pulmonary artery catheter to determine the correct dose to stop the heart for the required time of 20–30 s, this dose of adenosine 12 mg was then used on two occasions at the time of balloon inflation of the stent grafts. Pulse oximetry demonstrated that $Sp_{O_2}$ always exceeded 99% at this time and her temperature was 34.5 °C from environmental cooling only. There were no adverse complications of the use of adenosine. In the early postoperative phase the patient developed a small left basal pleural effusion, and at 6 days after

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operation she required a right brachial artery thrombectomy (10 cm thrombus) which was related most probably to the brachial artery sheath used for surgical access in that arm. She was discharged 10 days after her original aortic operation. Six month surgical follow-up showed that the aneurysmal sac had been isolated.

### PATIENT NO. 2

A 66-yr-old male presented with a recurrent thoracic aortic aneurysm just distal to the site of a previous open repair under cardiopulmonary bypass performed 3 yr previously for a chronic dissection. This first repair was immediately distal to the left subclavian artery. At angiography the coronary arteries were normal and there was normal ventricular function. The patient also had non-insulin dependent diabetes mellitus and glaucoma, and was receiving atenolol 100 mg, ramipril 5 mg and aspirin 100 mg mane, loratidine 10 mg daily, mebeverine 135 mg as needed, 0.25% timolol eye drops twice daily and temazepam 10–20 mg at night. Preoperative creatinine was 121 μmol litre$^{-1}$ (increasing to 182 μmol litre$^{-1}$ after operation), haemoglobin 121 g litre$^{-1}$ (decreasing to 73 g litre$^{-1}$, 2 days after operation, and then increasing to 92 g litre$^{-1}$, 4 days after operation, all without blood transfusion) and platelets $113\times10^9$ litre$^{-1}$ (decreasing to $64\times10^9$ litre$^{-1}$, 2 days after operation, and then increasing to $102\times10^9$ litre$^{-1}$, 4 days after operation). After premedication with papaveretum 15 mg and hyoscine 0.3 mg, anaesthesia consisted of placement of a thoracic extradural with the intention of using lignocaine to block the cardiac sympathetic nerves, tracheal intubation using thiopentone and tubocurarine/pancuronium block, and low-flow oxygen and nitrous oxide with isoflurane. Intra-arterial, pulmonary arterial, capillary wedge and central venous pressures were measured.

Surgical access was via the right common femoral artery. Adenosine was used at the time of balloon inflation to expand the stents in the descending thoracic aorta. Two grafts were used, one inside the distal part of the other (White-Yu GAD 30 mm×12.5 mm).[8] With the patient heparinized, receiving 100% oxygen, and after trial doses of 9, 15, 24, 36 and 45 mg administered peripherally via an arm vein to determine the correct dose to stop the heart for the required time of 20–30 s, a dose of adenosine 45 mg was used on each occasion at the time of balloon inflation to expand the stent grafts. The patient's oxygen saturation was never less than 100% at this time and his temperature was 35.5 °C, again solely from environmental conditions. There were no adverse complications of the procedure. The patient was nursed initially in the ICU with IPPV overnight. The tracheal tube was removed on the first postoperative day and the patient transferred to the ward on the second day and discharged from hospital on the fifth postoperative day. Six month surgical follow-up showed that the aneurysmal sac had been isolated.

### PATIENT NO. 3

A 51-yr-old male with Marfan's syndrome who had previously undergone two aortic valve replacements 17 and 12 yr earlier, and an abdominal aortic repair 10 yr previously, presented with acute dissection of his thoracic aorta which required a Bentall's procedure (replacement of the aortic valve and ascending aorta in continuity); 22 days later, while still in hospital, a further deterioration with interscapular back pain and angiographic and ultrasound evidence of a rapidly expanding thoracic aortic aneurysm required endoluminal repair. This endoluminal repair was immediately distal to the left subclavian artery. At angiography the coronary arteries were normal with moderately impaired left ventricular function. The patient was receiving i.v. heparin, and captopril 50 mg three times daily, sotalol 80 mg twice daily, diltiazem 240 mg mane, amiloride 5 mg mane, frusemide 40 mg twice daily, minoxidil 10 mg twice daily, atenolol 100 mg mane, digoxin 25 μg mane and allopurinol 300 mg mane. Preoperative creatinine was 67 μmol litre$^{-1}$ (increasing to 182 μmol litre$^{-1}$ after operation), haemoglobin 89 g litre$^{-1}$ (decreasing to 73 g litre$^{-1}$, 2 days after operation, and then increasing to 92 g litre$^{-1}$, 4 days after operation, all without blood transfusion) and platelets $365\times10^9$ litre$^{-1}$ (decreasing to $64\times10^9$ litre$^{-1}$, 2 days after operation, and then increasing to $102\times10^9$ litre$^{-1}$, 4 days after operation). After premedication with papaveretum 15 mg and hyoscine 0.3 mg, anaesthesia consisted of tracheal intubation using thiopentone and tubocurarine/pancuronium block and low flow oxygen and nitrous oxide with isoflurane. Intra-arterial, pulmonary arterial, capillary wedge and central venous pressures were measured.

Surgical access was via the left common femoral artery and right brachial artery. Adenosine was used at the time of balloon inflation to expand the stents in the descending thoracic aorta. Two grafts were used, one inside the distal part of the other (White-Yu GAD 24 mm×15 mm and 24 mm×7 mm).[8] With the patient heparinized, receiving 100% oxygen, and after trial doses of 9 and 15 mg administered centrally via the pulmonary artery catheter to determine the correct dose to stop the heart for the required time of 20–30 s, a dose of adenosine 21 mg was used on the first occasion and 27 mg on the second occasion at the time of balloon inflation to expand the stent grafts. The patient's oxygen saturation was never less than 100% at this time and his temperature was 35.5 °C, again solely from environmental conditions. There were no adverse complications of the procedure. The patient was nursed initially in the ICU but his trachea was not intubated or his lungs ventilated. The patient was transferred to the ward the next day and discharged from hospital on the fifth postoperative day.

## Discussion

Parodi, Palmaz and Barone[9] introduced endoluminal grafting of the aorta after animal experimentation by several groups,[10–14] and surgeons at our hospital have performed more than 150 abdominal aortic grafts.[15] Recently, repair of the thoracic aorta has also been performed by the endoluminal technique,[16 17] and this operation has required further evaluation of the place of hypotension at the time of expansion of the aortic stent to prevent both displacement of the stent and major damage to the aorta or undue strain on the myocardium leading to ischaemia or infarction.[18 19] If the stent is moved by the pressure of blood in the aorta forcing the inflating balloon distally at the time of expansion of the graft stent, there may be major problems in placement of the graft which is measured precisely before insertion. There may also be major problems, with aortic rupture or dissection, because of increased pressure in the aorta caused by balloon obstruction. The heart may also be stressed because of the increased demands on contractility and myocardial oxygen at the time of aortic obstruction by the balloon.[18 19] For endoluminal grafting of the abdominal aorta various anaesthetic hypotensive techniques, such as the use of sodium nitroprusside, glyceryl trinitrate, heavy volatile anaesthetic dose, and both lumbar and thoracic extradural block, have been used to reduce arterial pressure at the time of balloon inflation to expand the graft stent.

The work of Dorros and Cohn[20] during endoluminal grafting of the thoracic aorta suggested that adenosine would be an ideal agent to use to reduce arterial pressure by stopping the heart during surgical expansion of the proximal stent of the graft, which in these cases was to be by balloon inflation totally obstructing the thoracic aortic outflow. Adenosine occurs naturally in all cells, has no negative inotropic effects, has transient actions and decreases arterial pressure dramatically by causing asystole when given in high doses.[21] The pharmacology of adenosine is species specific but there appear to be two main adenosine receptors[21 22]—the $A_1$ receptor leading to inhibition of adenylate cyclase and thus decreased production of cAMP which is the dominant effect on cardiac electrophysiology[23] and the $A_2$ receptor leading to stimulation of adenylate cyclase and increased cAMP which is the dominant effect on vasodilatation. Recently in the rat there was a suggestion that there is a separate $A_3$ receptor mediating decreases in arterial pressure.[24] There are also effects on $K^+$ channels in the heart inducing an outward potassium current and hyperpolarization of the cell membrane.[23] Hepatic and renal insufficiency do not affect duration of action, as adenosine is taken up and metabolized by red blood cells and vascular endothelium, with a half-life of approximately 2–10 s in low doses but increasing with higher doses to approximately 2 min.[25–27] Adenosine either enters the nucleotide pool by phosphorylation to AMP or is metabolized primarily to inosine, hypoxanthine, xanthine and ultimately uric acid.[22] Side effects of adenosine are transient SA node inactivity, atrial fibrillation, hypotension and flushing, and in the awake patient headache, transient chest pain and dyspnoea.[5] In larger doses adenosine produces suppression of SA node automaticity which is short lived. Adenosine should be used with caution in patients with bronchial asthma because inhaled adenosine has precipitated asthma,[28] and in patients with sick sinus syndrome or second- or third-degree heart block unless there is a pacemaker inserted. Patients receiving methylxanthines are resistant to adenosine because of competitive inhibition of $A_1$ and $A_2$ adenosine receptors, and patients receiving dipyridamole may have prolonged asystole with adenosine because of inhibition of the transport system into cells, with subsequent increases in adenosine concentrations.[22 29] Slow channel calcium blocking agents such as verapamil and nifedipine also inhibit the transport of adenosine into cells.[30] Benzodiazepines enhance the effects of adenosine[22] and carbamazepine is reported in the company's product information leaflet also to increase the degree of heart block.

Potentially, patients who have endoluminal repair of the thoracic aortic may need to have this procedure converted to open surgical repair if there is sudden rupture of the diseased aorta by intra-aortic surgical manipulations or if there are other surgical problems with placement of the endoluminal graft. Thus anaesthesia techniques need to take such possibilities into account when preparing the patient for surgery. This was the main reason why our second patient had a thoracic extradural inserted, although extradural block of the cardiac sympathetics was also planned to assist with myocardial function, lower contractility and myocardial oxygen demand, and improve myocardial blood flow.[31] In addition, there may be a synergistic reduction in arterial pressure with administration of adenosine, which may prevent hypertension overcompensation on recovery from adenosine asystole.

Dorros and Cohn[20] recommended insertion of a temporary pacemaker before administration of adenosine. Our cardiological advice was that this was not necessary if an external pacing source was readily available, as it was most unlikely that the asystole would be prolonged in these patients who did not have any predisposing problems such as heart block or sick sinus syndrome.

The normal dose of adenosine for termination of supraventricular tachycardias is 3–6 mg and in some patients this dose has caused transient asystole. Larger doses cause some hypotension because of decreased peripheral vascular resistance even when asystole is not produced. The dose of adenosine to be used during expansion of the stent must be determined before the surgical manoeuvre, otherwise the duration of asystole and hence surgical time are unpredictable. Because the dose of adenosine required to produce asystole and the duration of asystole are unpredictable it is preferable to start with a dose of 9 mg, increasing in steps until asystole of the desired duration of approximately 20–30 s is produced. Our second patient proved relatively resistant requiring larger doses of adenosine than previously recommended,[20] but this may have been caused by administration of adenosine via a peripheral vein in this patient. Rankin and colleagues[32] showed that lower doses were needed (by a factor of one-third—3 mg *vs* 10 mg) when adenosine was administered centrally rather than peripherally, and we intend to give adenosine via a central vein in future. This patient was not receiving any drug therapy, such as methylxanthine, which has been reported to antagonize adenosine.[22] Another possible cause for the increased dose of adenosine in our second patient was the use of a thoracic extradural with full sympathetic block of the heart, as adenosine effects are reported to be more prominent when there is increased sympathetic tone.[33]

There were no apparent cardiac, vascular or neurological sequelae to cessation of cardiac output for periods up to 45 s in our patients who were not specifically protected by hypothermic techniques throughout surgery, although mild hypothermia occurred in both patients, which may have had some protective effect on cerebral metabolism.[34] Life-threatening events after adenosine would appear to be rare[35] and although minor side effects are common in awake patients, most of these symptoms and signs are masked during anaesthesia. The major complications which are possible after this technique using adenosine would be fatal arrhythmias, thromboembolism, cerebral ischaemia or infarction, coronary ischaemia or infarction, stroke or paraplegia. All of these complications are possible with any surgical repair of thoracic aortic aneurysms, and we believe that in the endoluminal surgical repair they may be less likely or at least no more likely to occur than in standard open repair of the thoracic aorta with or without cardiopulmonary bypass. Caution in the use of adenosine in this way to cause asystole intentionally should be exercised in patients with cerebrovascular or cardiac ischaemia which could potentially be exacerbated by the period of hypotension and circulatory arrest, although adenosine has been used for both cerebral and coronary protection against ischaemic damage.[36 37] These contraindications should be borne in mind when surgeons are contemplating the use of adenosine in endoluminal thoracic aortic repair, as Dorros and Cohn[20] have recommended that adenosine should be used in all aortic repairs by the endoluminal technique, including abdominal. White,[38] in a commentary on their article, cautioned that such sweeping recommendations may be "detrimental to the wider application and appeal of the endoluminal technique". In any case it would appear to be unnecessary in endoluminal repair of the abdominal aorta.[1 8 15]

We believe that the use of adenosine in considered cases of endoluminal repair of the thoracic aorta enhances the management of balloon inflation of the graft stent to allow better expansion to match the aortic diameter. This technique has the advantages of controlled transient hypotension with potential protection of the heart and brain.

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We thank Professor Jim May, Associate Professor Geoff White, and Drs Richard Waugh and Weiyun Yu for their cooperation.

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*British Journal of Anaesthesia* 1997; 78: 449–452

EQUIPMENT

# A new method for measurement of anaesthetic partial pressure in blood

M. A. SMITH, S. M. SAPSED-BYRNE AND G. G. LOCKWOOD

## Summary

We have developed a simple, reliable method for rapid analysis of the partial pressure of volatile anaesthetic agents, based on a two-stage, headspace analysis. It is designed to solve the problems associated with reduced solubility of modern anaesthetics. After equilibration and analysis of a 2-ml sample of blood at 37 °C, 1 ml is transferred to another vial for a second equilibration. This ensures that there is no vapour in the headspace before the second equilibration. Measurements were performed on human blood samples equilibrated with 1% sevoflurane, 2.5% isoflurane or 3% desflurane in a tonometer. The mean error in the sample measurements was −2.3% of the tono-meter reading and the 95% confidence interval for an individual measurement was ±8.5%. Blood samples may be stored overnight without any significant change in the results. (*Br. J. Anaesth.* 1997; **78**: 449–452).

**Key words**
Anaesthetics volatile, isoflurane. Anaesthetics volatile, desflurane Anaesthetics volatile, sevoflurane. Measurement techniques, partial pressure.

The rarity of clinical studies which measure partial pressures of anaesthetics in blood is a testimony to the troublesome nature of the assay. Blood content can be measured relatively simply by comparison, but partial pressure can be calculated only if the blood-gas partition coefficient is known. The classical headspace analysis technique for measurement of partial pressure involves equilibrating the anaesthetic between the blood sample and air (the headspace) within the containing vessel.[1 2] The partial pressure in the headspace can then be measured easily, but is no longer equal to the initial partial pressure in the blood sample. However, if the headspace is repeatedly flushed with fresh gas and repeated equilibrations performed, then a curve of the exponential washout of the anaesthetic from the blood can be plotted. Projecting this curve one step backwards from the first equilibration should give the initial partial pressure of the anaesthetic vapour. The blood-gas solubility of the sample can be determined from the rate of washout if the volumes of blood and headspace are known. Blood can be equilibrated within the glass syringe used to obtain the sample[1 2] (which has the advantage of maintaining ambient pressure in the headspace) or it can be transferred to a vial sealed with a PTFE-faced septum[3] (which has a cost advantage). If the ratio of air to blood is very small, such as when a bubble is introduced into a syringe of blood and allowed to equilibrate, the reduction in partial pressure of anaesthetic within the blood is negligible and a single step measurement is adequate.[4] We have found this technique troublesome in practice and in principle it is less appropriate for less soluble anaesthetics.

When we measured partial pressures using this classical technique our results grossly underestimated the partial pressure of desflurane in blood equilibrated in a tonometer, even though we were able to measure isoflurane partial pressures reasonably accurately. We thought that the error may be caused by trapping of desflurane in bubbles which prevented efficient flushing of the headspace between equilibrations. This would have a greater effect with desflurane than isoflurane because there is more desflurane in the gas within a bubble than in an equivalent volume of blood—the reverse is the case for isoflurane. We describe a simple method for accurate, reproducible and rapid analysis of the partial pressure of a volatile anaesthetic in small volumes of blood which does not depend on an assumed blood-gas partition coefficient.

## Methods

### EQUIPMENT

All gas samples were analysed using a Pye Series 204 gas chromatograph. The carrier gas was nitrogen flowing at 30 ml min$^{-1}$. A 0.9-m glass column (2 mm id) packed with 3% OV-17 on GasChromQ was maintained at 125 °C, producing a retention time of 0.5 min. The volatile agent was detected by a flame ionization detector operating at 175 °C. All samples were injected into a 20-µl sampling loop (Valco) on the chromatograph inlet using a 100-µl

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gas-tight syringe fitted with a valve (SGE, Melbourne).

Blood samples were prepared by equilibration in an IL-237 tonometer. A 2.5-ml gas-tight syringe (SGE, Melbourne) was used to transfer blood from the tonometer and between vials.

A cylinder of isoflurane in air was prepared and used as a standard to confirm stability of the gas chromatograph throughout the measurements. An approximate measurement of its concentration was made using a Datex Ultima (Datex Instrumentarium, Helsinki), calibrated according to the manufacturer's recommendations.

### PREPARATION OF BLOOD SAMPLES

Blood was obtained (with the approval of the chairman of the local Research Ethics Committee) from healthy volunteers and patients undergoing major surgery. A 6-ml blood sample was placed in the tonometer and allowed to equilibrate with a gas mixture flowing at 200 ml min$^{-1}$ for a period of 15 min. Mixtures of 1% sevoflurane, 2.5% isoflurane or 3% desflurane in air, and a mixture of 3% desflurane, 5% carbon dioxide and 21% oxygen (balance nitrogen) were used. A gas sample was obtained from the outflow of the equilibration chamber into the 100-µl syringe and injected into the gas chromatograph. This was taken to be the "true" partial pressure of anaesthetic in the blood. Two 2-ml aliquots of blood were then transferred accurately into nominally 5-ml vials (mean 4.77 (SEM 0.01) ml, measured by water displacement) and closed by a screw cap sealed with a Teflon-faced septum. The analysis was generally undertaken immediately but in order to investigate the effect of delay in measurement, one sample of some pairs was stored in a refrigerator and analysed 24 h later.

### ANALYSIS TECHNIQUE

The vials were agitated in a water bath at 37 °C for 1 min. Headspace gas was then sampled using a 100-µl syringe by puncturing the vial septum and making several movements of the plunger. Two samples were obtained and injected into the gas chromatograph: the greater reading (almost invariably the first, but differences were generally less than 2%) was used in the calculations. Exactly 1 ml of blood was transferred into another 5-ml vial and sealed with a new cap and septum for a second period of equilibration at 37 °C and subsequent analysis of the headspace gas (see fig. 1). The syringe was flushed several times with room air between samples to avoid carry over, and frequent air samples were injected into the gas chromatograph to confirm that syringe contamination was negligible.

### CALCULATIONS

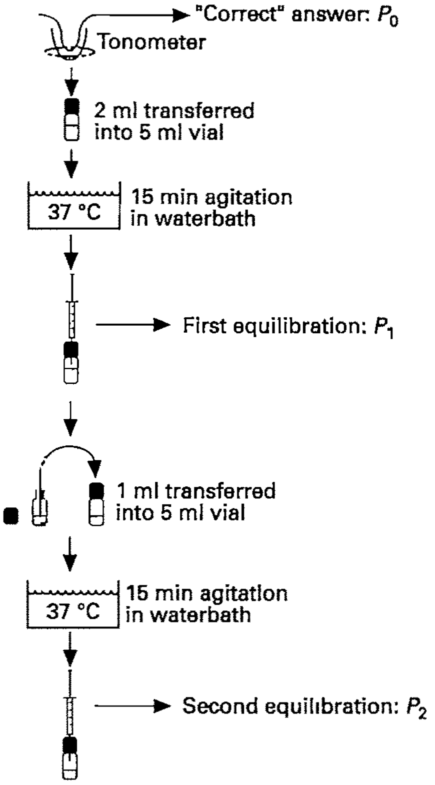
"Correct" answer: $P_0$
Tonometer
2 ml transferred into 5 ml vial
37 °C
15 min agitation in waterbath
First equilibration: $P_1$
1 ml transferred into 5 ml vial
37 °C
15 min agitation in waterbath
Second equilibration: $P_2$

*Figure 1* Methodology flowchart.

When the sample is equilibrated in the water bath the pressure within the headspace increases because of warming, humidification and exchange of gases with the blood sample. When the headspace sample is injected into the gas chromatograph it is at room temperature and pressure: the concentration of desflurane is unchanged but the partial pressure is reduced, so the chromatograph reading must be increased to compensate for this. The increase in pressure caused by temperature should be given by a factor of:

$$(273+37)\ /\ (273+T_{\text{lab}})$$

where $T_{\text{lab}}$=laboratory temperature in Celsius and typically gives a 5% increase. Humidification increases pressure by 6 kPa, but when the sample is aspirated into the chromatography syringe it cools and the vapour pressure of water reduces to approximately 3 kPa, and our calculations include this factor to correct for the "dilution" of the anaesthetic by water vapour in the headspace sample.

Carbon dioxide in blood also equilibrates with the headspace increasing the total headspace pressure. Some correction for this should be made, but the relationship between carbon dioxide content and tension is complex. We have crudely assumed that the content is 0.1 ml (ml of blood)$^{-1}$ kPa$^{-1}$. Then a 2-ml blood sample equilibrated with xkPa carbon dioxide contains 0.2x ml of carbon dioxide. After equilibration with 3 ml headspace the total vial carbon dioxide content is $0.2y+3y/101.3$, where y=carbon dioxide tension after equilibration in kPa. Assuming that no carbon dioxide is lost from the vial we deduce that $y=0.2x/0.23=0.87x$, so the pressure within the headspace increases by 0.87 of the fractional partial pressure of carbon dioxide in blood before the first equilibration. A similar effect occurs during the second equilibration, although the volumes of blood and headspace have changed, and we allow for an increase in headspace pressure of 0.63x at the time the second sample is obtained. Finally, the volatile anaesthetic itself increases the headspace pressure (although this is only likely to be important for desflurane). Conversion of gas chromatograph counts to partial pressure of the syringe sample ($P_{\text{syringe}}$) is achieved by sampling intermittently from a cylinder containing a known concentration of the vapour concerned. $P_{\text{syringe}}$ is converted to partial pressure within the vial ($P_{\text{vial}}$) by

$$P_{\text{vial}}=P_{\text{syringe}}\times 310\,/\,(273+T_{\text{lab}})\times(1+F_{\text{water}}+F\text{CO}_2+F_{\text{anaesthetic}})$$

where $F_{\text{water}}$ is taken to be 0.03, $F\text{CO}_2$=fractional carbon dioxide tension in the vial, and $F_{\text{anaesthetic}}$ is taken to be $P_{\text{syringe}}$ expressed as a fraction of ambient pressure.

Simple back projection no longer works because the ratio of blood to air is not constant. Let $P_0$ be the partial pressure of desflurane in the sample when it was first drawn; let $P_1$ and $P_2$ be the partial pressures in the vial after the first and second equilibrations, respectively; let $V_v$, $V_1$ and $V_2$ be the volumes of the vial, the first blood sample (2 ml) and the sample transferred (1 ml), respectively; let λ be the blood gas coefficient at 37°C. The gas chromatograph readings are corrected for pressure changes in the vial caused by humidification and warming of air. Then equating the amount of desflurane in the vial before and after each equilibration:

$$P_0V_1\lambda=P_1V_1\lambda+P_1(V_v-V_1)$$

and

$$P_1V_2\lambda=P_2V_2\lambda+P_2(V_v-V_2)$$

The second equation is solved for λ and this value is used to determine $P_0$ in the first. The calculations were performed using Microsoft Excel v4.

## Results

Data are presented as percentage of the tonometer concentration and are shown in figure 2. Analysis of variance revealed no difference between the results for the different anaesthetics. Overall the mean error of the 93 samples was 2.3%, with the 95% confidence interval of the mean (−3.2%, −1.4%) failing to include zero, that is there was a systematic error. The mean difference (confidence interval of the mean) between 11 paired samples analysed 24 h apart was 2.0% (−0.8%, +4.8%) of the tonometer reading.

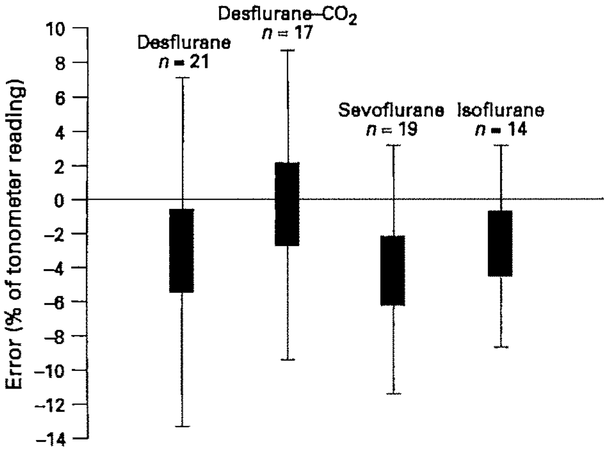

*Figure 2* Results from the four equilibration gas mixtures. The solid bars indicate the 95% confidence interval of the mean, the error bars indicate the 95% prediction interval for an individual measurement.

## Discussion

When we attempted to measure the partial pressure of desflurane using the method described by Landon and colleagues for isoflurane,[3] we consistently obtained values less than the tonometer. We blamed incomplete flushing of the headspace between equilibrations caused by trapping of desflurane vapour in froth and bubbles, noting that such errors are more significant the less soluble the agent. We therefore decided to transfer an aliquot of blood to a new vial to overcome this problem.

When the samples are equilibrated in vials it is necessary to allow for pressure changes in the headspace. Our corrections for this are exclusively based on simple, theoretical physical principles, yet they are not commonly used in this context. When a physiological concentration of carbon dioxide was present in the tonometer gas our results would have underestimated by approximately 5% without the appropriate correction factor. We have been able to ignore the exchange of oxygen between blood and sample because the carrier gas for the tonometer was air and the headspace also initially contains air. There may however be an effect if blood is not fully saturated with oxygen because uptake of oxygen by blood reduces absolute headspace pressure.

When multiple headspace equilibrations are used, successive measurements lie on an exponential washout curve and all points contribute to its determination. It is simple to calculate the best fit to such a function if the data are assumed to be homoscedastic, that is measurements at each equilibration have equal variances. We experimented with multiple sample transfers and washouts, but it seemed unlikely that our data would be homoscedastic given that blood volume was reduced at each step, and it was not clear how to weight the contribution of each equilibration in the new washout function. We therefore calculate the sample blood-gas coefficient from the results of the second equilibration and use that result with the first measurement to calculate the initial partial pressure of desflurane in the sample.

Although there is a systematic error in our application of this technique, it is small compared with the confidence interval for an individual measurement and it is even possible that equilibrium within the tonometer was incomplete. The important result for an individual sample is the interval about it within which the true value is expected to lie. The confidence interval of 8.5% of the reading for an individual sample may seem disturbingly wide, but it bears comparison with others in the literature. Fink and Morikawa[1] published their much quoted article without any results. Knill and co-workers[2] used their method with 10-ml blood samples tonometered with isoflurane equilibrated four times in syringes. Their duplicate samples agreed within 4.1% (cf. our 8.5%), but they did not test their technique against tonometered blood. Landon and co-workers[3] collected 0.5-ml specimens into 2-ml vials and performed four headspace equilibrations. When they tested this method using blood tonometered with 0.24% isoflurane they found a mean error of less than 1% of the true value and a variability similar to ours in absolute terms, but because we used 1% isoflurane in the tonometer, our variability was less as a proportion of the true value. Dwyer and co-workers[5] performed two headspace equilibrations of 5-ml samples within syringes and found a systematic error of −4±7% (cf. our −2.3±8.5%) when measuring blood equilibrated with isoflurane in a tonometer. Several groups have used a single headspace equilibration to determine the partial pressure of gas within the sample. The headspace measurement is related to initial partial pressure by a nomogram which either relies on an assumed blood-gas coefficient or requires tonometry of a separate blood sample with a known gas mixture. This presents problems if the blood-gas coefficient is variable (e.g. during cardiopulmonary bypass). Frei and co-workers[6] described a technique of single headspace equilibration of 0.5 ml of blood in a 5-ml vial. When measuring isoflurane they obtained a coefficient of variation of 2.8% (c.f. our 4.3%). Their method allows one analyst to process 40 samples per hour using a given nomogram. Flynn and co-workers[7] injected each of five 5-ml vials with 0.6 ml of blood from the same sample, taking the mean value as the result for that sample. They claimed a coefficient of variation of less than 4% for isoflurane, which was less than the error in the slope of their nomogram (1.93±0.11). Katoh and colleagues[8] measured sevoflurane partial pressures in arterial blood from a single headspace equilibration. They measured the blood-gas solubility in each case by obtaining a blood sample before anaesthesia and equilibrating it with a known amount of sevoflurane vapour, but did not validate their technique.

In summary, the two-stage method described in this article allows rapid measurement of the partial pressure of desflurane and blood-gas solubility in a single 2-ml sample of blood with accuracy and repeatability similar to published results on the measurement of isoflurane.

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*British Journal of Anaesthesia* 1997; **78:** 453–475P

ABSTRACTS

# Proceedings of the Anaesthetic Research Society

NORTHWICK PARK MEETING

November 21–22, 1996

(The name of the author presenting the paper is shown in bold type. *Indicates non-member.)

All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review Committee

## Modifying infant stress responses to major surgery: spinal *vs* extradural *vs* opioid analgesia

**A. R. Wolf** and E. Thomas*
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In a previous infant study we have shown that extradural analgesia suppresses stress responses to major surgery better than analgesic doses of opioid.[1] Adult work suggests that spinal analgesia may be better than extradurals.[2] We therefore wished to determine if this was true in infants undergoing major surgery.

After appropriate consents, we studied 26 infants undergoing intrabdominal or thoracic surgery. Patients were anaesthetised in a standardized fashion with isoflurane in 30% oxygen. Before surgery, patients were randomized to receive one of three analgesia regimens: Group 1 (n=10) single dose spinal of 0.5% heavy bupivacaine (0.1 ml $kg^{-1}$) plus extradural catheter placement, Group 2 (n=8) extradural analgesia with an initial dose of 1 ml of 0.25% bupivacaine (with additional increments), Group 3 (n=8) i.v. fentanyl (1 $\mu g$ $kg^{-1}$ with additional increments). Additional analgesia (extradural bupivacaine groups 1 and 2, i.v. fentanyl Group 3) was administered if arterial pressure rose 20% above baseline values. Blood samples for glucose and catecholamines were taken after induction, 45 min and at the end of surgery. Heart rate and arterial pressure were recorded at 5-min intervals. Group comparisons for parametric data were made using repeated means analysis (Manova).

Groups were matched for ages and weights. Heart rate increased significantly ($P<0.05$) with the start of surgery in groups 2 and 3, but not Group 1. Systolic arterial pressure in Group 1 decreased from a mean of 94.6 (SD 19 mm Hg) before induction to 76.1 (SD 18.4) after administration of spinal bupivacaine. Plasma glucose concentrations during surgery are shown in figure 1 for the three groups. Repeated measures analysis indicated a significant group effect ($P<0.05$) in the order opioid> extradural>spinal. Adrenaline concentrations rose during surgery in a similar fashion, but failed to achieve statistical significance owing to large interpatient variability and small sample size. Noradrenaline concentrations decreased significantly during surgery in Group 1. This study suggests that spinal anaesthesia may be better than extradural anaesthesia in obtunding cardiovascular and metabolic responses to surgery and highlights the value of routine intraoperative glucose estimations.

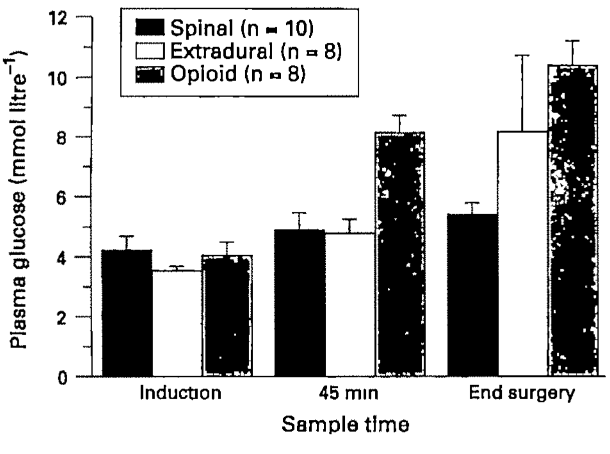

*Figure 1* Glucose response to surgery for spinal, extradural and opioid treatment groups. Values are expressed as means (SEM)).

**Key words**
Anaesthesia, paediatric. Anaesthetic techniques, spinal.

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## Early clinical evaluation of diaspirin cross-linked haemoglobin in major surgery: a pilot study

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Diaspirin cross-linked haemoglobin (DCLHb) is a tetramer of chemically crosslinked α subunits of stroma-free haemoglobin. DCLHb carries oxygen. In volunteers it combines a vasopressor effect with a colloid osmotic effect similar to 5% albumin solution DCLHb contains no blood group antigens or cell components.

In this prospective randomized single blind study we enrolled 20 ASA I–II patients undergoing major surgery with an expected blood loss of >1000 ml. Patients were selected randomly to receive either 50 mg $kg^{-1}$ of 10% DCLHb or an equivalent volume of 0.9% NaCl, administered after induction and before surgical incision. Pre- and post-infusion laboratory investigations included FBC, U and E and creatinine, LFT, haptoglobin, haemopexin, free haemoglobin, amylase and antibodies to DCLHb. Haemodynamic data were obtained by invasive monitoring (arterial, CVP) and transthoracic bioimpedance

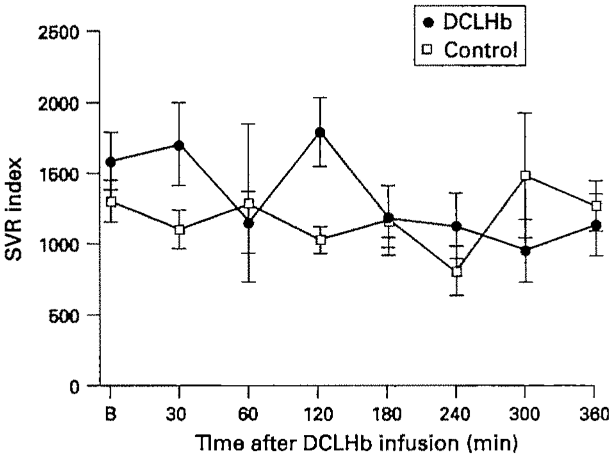

*Figure 2* Changes in systemic vascular resistance (SVR) with time. The MAP difference was correspondingly significant. This difference disappeared after 3 h. AUC: SVRI $P=0.024$

(BOMED) We recorded AP, HR, CO, CVP, $Sp_{O_2}$, urinary output, fluid replacement and transthoracic impedance (thoracic water). Safety end-points were renal failure, myocardial ischaemia and liver dysfunction.

There were no differences in any other haemodynamic or laboratory measurements. There were no outcome differences between groups (fig. 2).

This pilot study shows that DCLHb has short-lived vasopressor effects which may be of physiological value in major surgery. There were no adverse effects on haemodynamic variables or laboratory tests of organ function. A follow-up study to investigate the efficacy of DCLHb in tissue oxygenation and outcome is indicated.

**Key words**
Blood, substitutes. Blood, haemoglobin.

**Acknowledgement**

We thank Baxter Healthcare for financial support.

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## Effect of different respiratory patterns on respiratory sinus arrhythmia in conscious volunteers

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Respiratory sinus arrhythmia (RSA) has been proposed as a measure of anaesthetic depth.[1] We have measured RSA and heart rate variability (HRV) in order to test whether substantial alterations in respiratory pattern affected the level of RSA while level of consciousness was unchanged.

Six male volunteers breathed air at tidal volumes of 5 and 10 ml $kg^{-1}$ with I:E ratio of 1:1, 1:2 and 2:1. Breathing was synchronized by an electronic metronome at 45 beat $min^{-1}$. Normocapnia was maintained by the addition of dead space. The six experimental periods of 10 min followed periods of stabilization. Raw ECG was digitised at 1000 Hz using a CED 1401 plus interface and Spike 2.01 software (Cambridge Electronic Design Ltd). ECG was inspected visually to exclude artefact and R waves was detected by templating. Respiration was measured using a flow meter (FDE Magtrak) linked to the interface. RSA was calculated using the method of Pomfrett and colleagues[1] to determine the R statistic. In order to determine independently the level of HRV, power spectral analysis of the ECG was performed by 256 point fast Fourier transformation of the ECG tachygram re-sampled at 4 Hz. The area under the curve of the low frequency (LF) peak (0.08–0.156 Hz) and high frequency (HF) peak (0.218–0.281 Hz for I:E=1:2 and 2:1, 0.328–0.406 for I:E=1:1) were measured. Note that the position of the HF peak varies with respiratory rate.

*Table 1* Mean R, low frequency (LF) are and high frequency (HF) area (SD). Mean R was not significantly altered by changes in tidal volume or I:E ratio, paired *t*-test

| | Mean R (dimensionless) | LF area ($Hz^2 \times 10^{-5}$) | HF area$\times 10^5$ ($Hz^2 \times 10^{-5}$) |
|---|---|---|---|
| 5 ml $kg^{-1}$: | | | |
| I:E 1:1 | 0.179 (0.068) | 5.41 (5.0) | 3.95 (2.4) |
| 1:2 | 0.193 (0.048) | 6.75 (5.4) | 4.44 (2.6) |
| 2:1 | 0.270 (0.013) | 7.23 (5.2) | 3.56 (1.9) |
| 10 ml $kg^{-1}$: | | | |
| I:E 1:1 | 0.197 (0.046) | 6.58 (8.7) | 2.68 (9.8) |
| 1:2 | 0.256 (0.071) | 7.98 (5.2) | 8.72 (7 6) |
| 2:1 | 0.270 (0.012) | 6.87 (6.0) | 5.24 (3.9) |

Substantial changes of tidal volume and I:E ratio failed to alter these measures of RSA in conscious volunteers (table 1). This investigation could be usefully repeated in anaesthetized patients.

**Key words**
Arrhythmia, sinus.

**Reference**

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## Effect of halothane and sevoflurane on slowly adapting lung receptors in the rabbit

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We compared the effect of halothane and sevoflurane on the discharge frequency of slowly adapting receptors (SARs) in the lungs of rabbits using a single nerve fibre recording technique.

Halothane, enflurane and isoflurane were studied in the past[1] and were found to raise the threshold of firing of lung SARs, while at the same time increasing their discharge frequency above this threshold. No quantitative difference was found between these agents. Sevoflurane has not been studied but is known to be much less irritant to the airways,[2] and therefore its effect on lung receptors may be different from other agents.

Four New Zealand White rabbits were studied. Each received 25% urethane 7 ml $kg^{-1}$, with vecuronium 0.2 mg $kg^{-1}$ and its lungs were ventilated with a tidal volume of 6 ml $kg^{-1}$ at a rate of 80 beat $min^{-1}$ Both vagi were divided and the left was desheathed and repeatedly split into thin filaments from which recordings were made, until a filament was found containing a single nerve fibre arising from a lung SAR. The lungs were then ventilated with oxygen containing sevoflurane or halothane at end-tidal concentrations of 2.0% followed by 5%. A number of receptors from each rabbit were studied. Recordings were made of tidal volume, airway flow and pressure, arterial pressure, heart rate and nerve fibre discharge frequency. Comparisons were made using two-factor repeated measures analysis of variance.

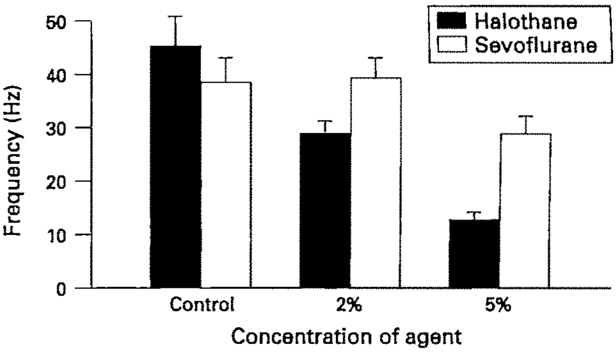

*Figure 3* Discharge frequency during expiration of slowly adapting receptors exposed to volatile agents (mean (SEM)).

Recordings were made from 19 slowly adapting receptors. We found that increasing agent concentration significantly decreased the frequency of discharge of the receptors during expiration ($P<0.0005$) (fig 3). The decrease caused by halothane was significantly larger than that caused by sevoflurane ($P<0.0005$). However, we found no significant effect of either agent on the discharge frequency of the receptors during the final 100 ms of inspiration, when discharge frequency is at a maximum.

**Key words**
Anaesthetics volatile, sevoflurane. Lungs, slowly adapting receptors. Rabbit.

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## Anaesthetic and sedative agents suppress neutrophil interleukin-8 release

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Immune suppression is common in postoperative patients and those on intensive care. Trauma and surgical stress modify the immune response. However, anaesthetic and sedative agents also affect some aspects of immune function. Interleukin-8 (IL-8) is a chemotactic and activating factor produced by neutrophils and induces the expression of adhesion molecules, enhancing neutrophil adhesion to the endothelium. We investigated the effect of anaesthetic agents on neutrophil production of IL-8. Isolated human neutrophils were exposed to varying concentrations of propofol or midazolam in the presence of lipopolysaccharide $1.7\ \mu g\ ml^{-1}$. After 20 h, IL-8 was measured in culture supernatants using ELISA. Data were analysed using Kruskal-Wallis analysis of variance.

Both propofol ($P=0.006$) and midazolam ($P=0.05$) suppressed neutrophil IL-8 accumulation at sedative concentrations (fig. 4). Northern analysis revealed increased mRNA for IL-8 at the highest concentrations of both agents. Interaction of released IL-8 with cell surface receptors may affect the appearance of mRNA within the cell and that decreased release of IL-8 in response to anaesthetic agents therefore results in increased mRNA for IL-8. The precise mechanism requires further investigation. Neutrophils themselves augment neutrophil recruitment and activation through local production of IL-8 thus amplifying antimicrobial defence. Suppression of this process by anaesthetic and sedative agents may predispose postoperative and intensive care patients to infection.

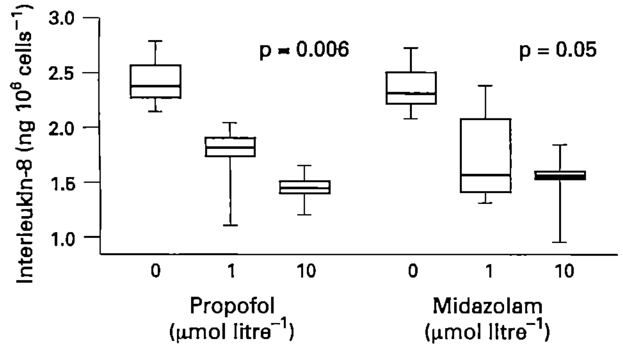

*Figure 4* Effect of propofol/midazolam on lipopolysaccharide-stimulated IL-8 production by neutrophils. Bars are median and 25th and 75th percentiles with range shown as vertical lines. Data were from between 6 and 8 separate experiments.

**Key words**
Anaesthetics i.v. Hypnotic benzodiazepines, midazolam. Blood, neutrophils.

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## Effect of exogenous nitric oxide/superoxide on interleukin-8 from human neutrophils

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Patients with acute inflammatory lung injury are commonly treated with inhaled nitric oxide. Such patients have increased concentrations of the chemotactic/activating factor interleukin-8 (IL-8) in their bronchoalveolar lavage fluid leading to the accumulation of neutrophils. These activated cells produce superoxide and proteases, causing lung damage. There is limited evidence to suggest that nitric oxide donors may regulate IL-8 expression in some cell types. The effects of inhaled nitric oxide on mediators of inflammation in the lung are not known. We investigated the effect of a nitric oxide donor and a combined nitric oxide/superoxide (and hence peroxynitrite) donor on lipopolysaccharide (LPS)-mediated accumulation of IL-8 from cultured human neutrophils.

Cells were isolated using a single step density gradient and incubated with and without LPS for 20 h in the combined presence of a range of concentrations of the combined nitric oxide/superoxide donor 3-morpholinosydnonimine (SIN-1) or the nitric oxide donor, 1,2,3,4-oxatriazolium, 5-amino chloride (GEA-3162). IL-8 was measured in culture supernatants using enzyme immunoassay. IL-8 accumulation from LPS-stimulated neutrophils was significantly and dose-dependently decreased by SIN-1 ($P=00065$, Kruskal-Wallis ANOVA). Basal IL-8 accumulation from unstimulated cells was also decreased by SIN-1 ($P<0.01$, Mann-Whitney $U$ test) (fig. 5). In contrast, GEA-3162 increased IL-8 in both LPS-stimulated ($P=0.02$, Kruskal Wallis) and unstimulated neutrophils ($P<0.02$, Mann-Whitney).

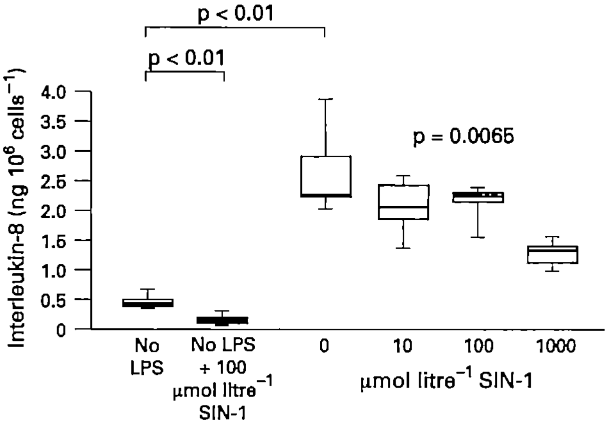

*Figure 5* The effect of SIN-1 on IL-8 accumulation from PS stimulated neutrophils. Plot is median, and 25th and 75th percentiles with range shown as vertical bars. Data are from six experiments.

Nitric oxide and superoxide have profound effects on IL-8. The transcription factor NFκB regulates IL-8 expression. Nitric oxide has been shown to activate NFκB in some cell types, but acts as an inhibitor in other cells. The effect of peroxynitrite on NFκB is not known. Selective down-regulation of IL-8 within the lung is likely to reduce neutrophil accumulation and may be beneficial. These results may have implications for the treatment of patients with acute lung injury with inhaled nitric oxide.

**Key words**
Pharmacology, nitric oxide. Blood, neutrophils. Polypeptides, cytokines.

**Acknowledgement**

B.H.C. is an Association of Anaesthetists and RCA Intavent research fellow.

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## Adhesion molecule concentrations in arterial and jugular venous serum after acute brain injury

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Induction of pro-inflammatory cascades after acute brain injury, with infiltration of leucocytes into brain tissue, results in secondary damage. Adhesion molecules, which are expressed on the surface of leucocytes and endothelial cells, have an important role in the migration of leucocytes into tissue after injury. L-selectin is believed to control light adhesion of leucocytes to the endothelium, whereas intercellular adhesion molecule-1 (ICAM-1) mediates later firm attachment. We hypothesized that an upregulation of ICAM-1 and L-selectin expression after acute brain injury would result in elevated serum concentrations of these molecules, with jugular venous concentrations being greater than arterial.

We investigated arterial and jugular venous (JV) concentrations of soluble ICAM-1 and soluble L-selectin, in 32 patients (22 with traumatic brain injury and 10 with spontaneous subarachnoid haemorrhage) admitted to the intensive care unit (ICU). Paired arterial and JV blood samples were taken at designated times after

*Table 2* Mean arterial concentrations at difference times

| | ICAM-1 (ng mg$^{-1}$) | | | L-selectin (ng ml$^{-1}$) | | |
|---|---|---|---|---|---|---|
| Time | Mean | 95% CI | *P* value* | Mean | 95% CI | *P* value* |
| Control | 254 | 217–290 | | 904 | 814–994 | |
| Admission | 272 | 223–322 | 0.532 | 625 | 565–685 | <0.0001 |
| 24 h | 273 | 235–313 | 0.436 | 573 | 529–616 | <0.0001 |
| 48 h | 316 | 267–365 | 0.040 | 591 | 536–645 | <0.0001 |
| 96 h | 448 | 339–557 | 0.002 | 569 | 505–634 | <0.0001 |

*Two tailed *t*-test, patient samples *vs* control. Control samples are venous.

brain injury: on admission, at 24 h, 48 h and 96 h. Analysis of serum for L-selectin and ICAM-1 was performed by ELISA. A total of 220 samples (110 pairs) were analysed in duplicate for each adhesion molecule. Serum samples were taken from 12 apparently healthy volunteers to be used as controls.

Median time from primary insult to admission sample was 8 h 30 min (range 2–14 h). Median age was 37 (range 17–69) yr. Median Glasgow Coma Score was 7 (range 3–15).

For ICAM-1, mean arterial concentration at each of the time points after injury is shown in table 2 (ANOVA, $P<0.001$), with the concentration at 96 h being significantly higher than at the other time points ($P=0.001$, $P<0.001$, $P=0.014$ respectively). Mean JV-arterial difference was 6.9 ng ml$^{-1}$ (95% CI [−4.5–18.3], $P=0.31$). For L-selectin, mean arterial concentrations are shown in table 2 (ANOVA $P=0.40$). Mean JV-arterial difference was 3.6 ng ml$^{-1}$ (95% CI [−8.0–15.2], $P=0.60$).

We have found serum concentrations of ICAM-1 to be elevated at 48 h after acute brain injury, and to be elevated further at 96 h. This is in contrast with an unexpected decrease in serum L-selectin from normal values from the time of admission. No differences between jugular venous and arterial concentrations were found. Increased serum concentrations of soluble ICAM-1 have been reported in many inflammatory disease states including septic shock[1] and bacterial meningitis. Elevated serum concentrations of L-selectin have also been reported in sepsis and cerebral malaria A recent study[2] also reported a decrease in serum concentrations of L-selectin in adult respiratory distress syndrome. this may be a result of sequestration of L-selectin by activated endothelium. Although the cerebral vasculature is structurally different from the systemic vasculature, the pathophysiology of the inflammatory process after a primary insult may be similar.

**Key words**
Brain, injury. Brain metabolism.

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## Effect of local anaesthetic agents on *in vitro* proliferation of human dermal fibroblasts

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Local anaesthetic agents are commonly infiltrated into the skin to produce per- or postoperative analgesia. Although fibroblasts are known to play pivotal roles in cutaneous wound healing and scarring, there have been few studies of how local anaesthetic agents influence dermal fibroblast proliferation. One study concluded that lignocaine and ropivacaine inhibit *in vitro* fibroblast proliferation in a dose-dependent manner.[1] It is recognized that age, sex and health status are important determinants of fibroblast behaviour, but most human fibroblast studies performed *in vitro* on donor specimens have failed to control for these variables.[2] This study assessed, first, the influence of donor age and, second, the differences between lignocaine and bupivacaine, on *in vitro* proliferative capability of dermal fibroblasts after exposure to clinically relevant concentrations of both agents.

*Table 3* Mean (SD) proliferation of human dermal fibroblasts when cultured in different concentrations of local anaesthetic agent as measured by $^3$H-thymidine incorporation, expressed as % counts min$^{-1}$ of control. *$P<0.05$ when old compared with young for same concentration of lignocaine or bupivacaine; †$P<0.05$ when equimolar concentrations of bupivacaine and lignocaine are compared within same age group

| | Young | Old |
|---|---|---|
| Lignocaine 1 μmol litre$^{-1}$ | 77 (17.1) | 22 (8.5)* |
| Lignocaine 10 μmol litre$^{-1}$ | 61 (10.7) | 14 (5.2)* |
| Lignocaine 100 μmol litre$^{-1}$ | 54 (14.5) | 9 (3.4)* |
| Bupivacaine 1 μmol litre$^{-1}$ | 98 (14.9) | 55 (13.8) |
| Bupivacaine 10 μmol litre$^{-1}$ | 77 (10.4) | 33 (8.4)*† |
| Bupivacaine 100 μmol litre$^{-1}$ | 61 (15.5) | 21 (6.6)*† |

Primary cultures of human dermal fibroblasts were obtained from explant cultures of dermis excised from the inner aspect of the upper arm of five young (20–30 yr) and 5 old (60–70 yr) healthy male volunteers. The cells were cultured in Dulbecco's modified Eagle's medium containing 10% fetal calf serum and antibiotics at 37 °C, and used for experiment after four to six passages of cell growth. The cells were seeded in 96-well plates (2×10$^4$/well) and allowed to attach for 24 h before 12 h of serum starvation. The fibroblasts were then exposed to lignocaine or bupivacaine, diluted in serum-free medium to concentrations of 1, 10 or 100 μmol litre$^{-1}$, for 4 h. $^3$H-thymidine was added to produce a final concentration of 0.5 μCi ml$^{-1}$. After 24 h, the cells were rinsed and the radioactivity was measured using a liquid scintillation counter. The studies were repeated in triplicate. Student's *t*-test (unpaired or paired) was used for statistical analysis of the data.

Fibroblast viability was not affected by any of the local anaesthetic concentrations used. Both lignocaine and bupivacaine inhibited fibroblast proliferation in a dose-dependent manner. At each concentration of local anaesthetic agent, inhibition of fibroblast proliferation was significantly greater for those donated from old subjects compared with those from young subjects. For fibroblasts from young subjects, there was no significant difference in proliferation after exposure to equimolar concentrations of lignocaine or bupivacaine. However, in fibroblasts from old subjects, there was significantly greater inhibition of proliferation with lignocaine compared with equimolar concentrations of bupivacaine.

After *in vitro* exposure to clinically relevant concentrations of lignocaine or bupivacaine, inhibition of proliferation is greater for fibroblasts donated from old subjects compared with those from young subjects (table 3). In equimolar concentrations, lignocaine inhibited proliferation of fibroblasts from old subjects more than bupivacaine. However, there was no difference between the two agents in inhibition of proliferation for fibroblasts from the young. This study only describes changes in fibroblast numbers and does not indicate changes in fibroblast function.

**Key words**
Anaesthetics local, Skin, fibroblast

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## Nested case–control study of risk factors for cardiovascular death after anaesthesia and surgery

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We report a case-control study of risk factors for cardiovascular death after anaesthesia and surgery. This study was nested within the Oxford Record Linkage study (ORLS). This is a large epidemiological study which collects data on all hospital care delivered within the area previously encompassed by the Oxfordshire Regional Health Authority.

Patients undergoing elective surgery under general anaesthesia in five hospitals within the ORLS between 1979 and 1990 constituted the study population. The ORLS was interrogated to identify patients aged over 18 yr who died within 30 days of surgery, and who had a cardiovascular cause of death recorded on their death certificate (ICD9 codes 401 to 438 inclusive, but excluding 415.1 which is pulmonary embolism). Patients undergoing cardiac and neurosurgery were excluded. For each case a control patient matched on age, sex, type of surgery and consultant was identified. As required by the local Ethics Committee, consent was obtained from the consultant in charge of each patient's care for the ORLS to identify individual patients, and for the medical records of these patients to be examined. Data on cardiovascular risk factors and history of cardiovascular disease were collected from the medical records of each patient. The associations between various potential risk factors and postoperative cardiovascular death were examined using conditional logistic regression.

One hundred and ten case-control pairs were identified; 70 (64%) of the cases were male. the mean age of the cases was 72.0 (SD 19.55) yr and that of the controls was 71.0 (SD 10.26) yr. The final regression model is summarized in table 4.

*Table 4* Results of conditional logistic regression analysis

| | Odds ratio (95% confidence limits) | z (Wald test) | *P* value |
|---|---|---|---|
| Hypertension | 2.29 (1.17–4.50) | 2.41 | 0.016 |
| Myocardial infarction | 3.63 (0.94–4.50) | 1.87 | 0.062 |
| Heart failure | 2.15 (0.81–5.72) | 1.54 | 0.13 |
| Cerebrovascular accident | 1.73 (0.53–5.69) | 0.90 | 0.37 |
| Angina | 1.17 (0.39–4.30) | 0.24 | 0.81 |

Only the effect of hypertension reached significance at the conventional 5% level, although the data also give support for an effect of previous myocardial infarction.

**Key words**
Complications, perioperative cardiovascular mortality. Case-control study.

**Acknowledgements**

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## Randomized trial of hypotensive anaesthesia on cardiac, renal and cognitive outcome after total hip replacement

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The use of hypotensive anaesthesia in elderly high-risk patients is controversial owing to the perceived risks of stroke, myocardial infarction or renal dysfunction. This is a study of hypotensive extradural anaesthesia in elderly high-risk patients.

Following institutional review board approval, 235 patients gave informed consent to receive either hypotensive or normotensive extradural anaesthesia (mean arterial pressure (MAP) 50 mm Hg *vs* 65 mm Hg) throughout surgery. The study design was randomized and double-blinded, as people collecting postoperative data were not aware of the patients' treatment group. Entry criteria were 70 yr of age or older, or 60 yr of age or older with a history of either hypertension or ischaemic heart disease. All patients had a preoperative assessment which included a battery of 10 cognitive function tests[1] which were repeated 6 months after operation. After surgery, renal function and myocardial ischaemia/infarction were screened using predefined criteria.

Myocardial infarction or ischaemia occurred in 6% in the low MAP group and 4% in the higher MAP groups. Corresponding rates for renal dysfunction were 0.85% and 4%, respectively. Long-term cognitive disturbances were 5% and 11% in the low and higher MAP groups, respectively. Five percent of patients required homologous blood transfusion in the low MAP group, and about 6% in the higher MAP group. None of these differences were significant.

Hypotensive extradural anaesthesia, as used in this study, does not increase the rate of renal function, cardiac or cognitive complications in elderly high-risk patients.

**Key words**
Anaesthesia, hypotensive. Outcome, cardiac. Outcome, renal. Outcome, cognitive.

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## Audit of patients' attitudes to consent to clinical trials in anaesthesia

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Every patient has a right to determine what treatment he or she should receive. When an intervention may not directly benefit the patient, as in clinical trials, informed, freely given consent is all the more important. Over a period of 2 years, 204 patients consented to inclusion in one of six clinical trials in anaesthesia. One of three doctors explained the trial to them and left an information sheet which stated that participation was voluntary, their other treatment would not be affected and that they could change their minds at any time. Three were drug company-sponsored multi-centred trials ($n=44$) and had a three-page information sheet, the others were "in-hospital" trials ($n=160$) and the information sheet was one side of A4. We have audited patient satisfaction with the way they were approached and the information they were given.

The text of the information sheets was scored for readability using Flesch reading ease and Flesch-Kincaid grade level (Microsoft Word version 6.0.1). All the patients were sent a questionnaire with a covering letter. If no reply was received after 4 weeks a further letter and questionnaire were sent.

Readability scores of the in-house and the sponsored trial information sheets were similar. We received 158 (77%) completed replies, we were unable to find a current address for 12 (6%) and two patients declined to complete the questionnaire.

There were no significant differences in responses between the in-house and sponsored trial patients (Fisher's exact test). Twenty nine (14%) did not remember seeing an information sheet; of those that did 99% felt it was easy to read and understand and 94% felt it was an accurate description of what happened to them.

Five patients said that they had felt pressurized to take part. Three said that this was because they had been approached in a stressful situation before major surgery, one had a brother who died under anaesthesia but felt that she should take part to help other people and the last made no comment but did state later in the questionnaire that she felt her treatment had been improved by taking part in the trial.

Although most (154 (97%)) were aware that participation was entirely voluntary and that their treatment would not be affected by their decision only 131 (83%) were aware that they could change their minds at any time after giving consent. When asked if they would have liked to have been warned about the trial before coming into hospital 64 (41%) would have, 80 (51%) would not and 14 (8%) were unsure.

In conclusion, patient satisfaction with the consent process was not improved by increasing the volume of information given. We have shown that patients do not always have good recall for information given to them while in hospital but in general our patients were happy with the way they were approached and the information given. As anaesthetists involved in research it is very difficult to see prospective patients other than immediately before surgery and inevitably some people will find this a stressful time and will not be receptive to other interventions.

**Key words**
Physician–patient relationship. Medico-legal, informed consent.

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## Point mutation in the channel lumen of a GABA$_A$ receptor regulates modulation by isoflurane

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GABA is the most important inhibitory transmitter in the mammalian brain and the pentameric GABA$_A$ receptor/chloride channel is an acknowledged target for a broad range of anaesthetic drugs.[1] We recently described the upregulation of GABA activated chloride currents through the *Drosophila* RDL receptor and its ion channel mutant (which is insensitive to picrotoxinin) by clinical concentrations of isoflurane.[2] In this study we have examined the dose-dependence of anaesthetic interaction with both wild-type (WT) and mutant (MUT: bearing a point mutation in the M2 domain) RDL channels.

cDNA samples (Cornell University) were transcribed *in vitro*, then expressed in *Xenopus* oocytes using established techniques.[2] Ion channels were examined 1 to 2 days later using two-electrode voltage-clamp. GABA was applied for 5–15 s by throughput perfusion (around 10 ml min$^{-1}$). Concentration-response curves were plotted by a point-to-point fit before and after equilibration with isoflurane. Statistical assessment was by two-tailed Student's *t*-test, where appropriate. All reported observations are based on a minimum of three replicated experiments.

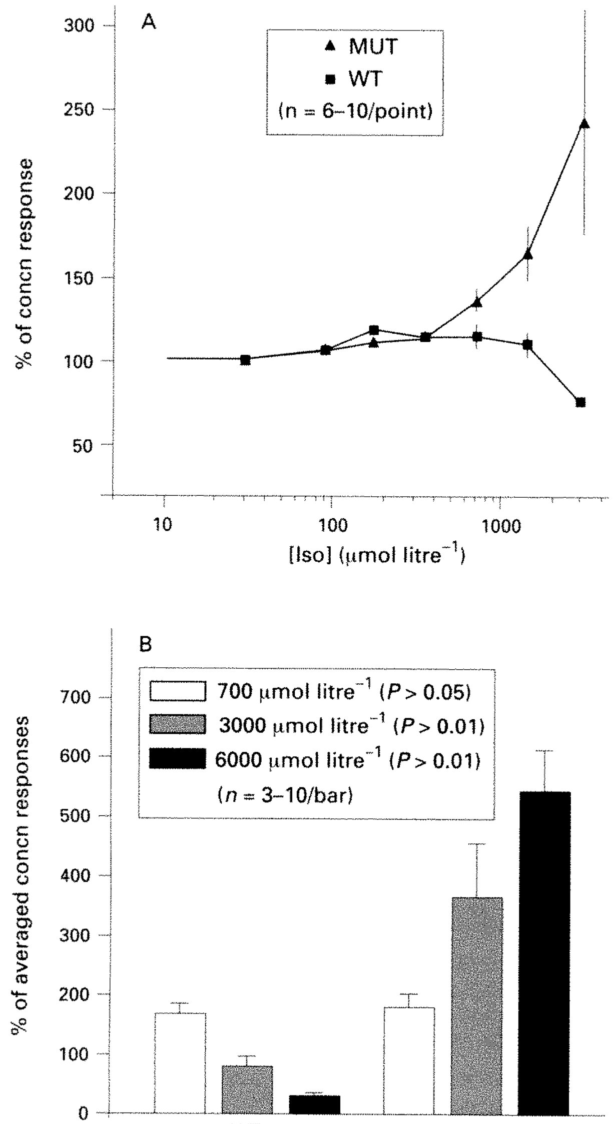

*Figure 6* Dose-dependent effects of isoflurane on GABA-evoked responses. (Bars represent SEM.)

Preliminary studies indicated that isoflurane (350–700 μmol litre$^{-1}$) enhanced subsaturating GABA-induced conductances: equilibrium was attained within 5 min of onset and responses reversed within 10 min of washout ($n$=6). The effect of varying concentrations of isoflurane, over the range 30–3000 μmol litre$^{-1}$, was examined on both receptor isoforms at a fixed GABA concentration (EC$_{25}$: 5.62 μmol litre$^{-1}$). Both isoforms of the receptor were weakly upregulated by anaesthetic 175–700 μmol litre$^{-1}$. However, at concentrations of 1–3 mmol litre$^{-1}$, a drastic divergence in modulatory effect was evident: WT receptor conductances resulted in bell-shaped curves due to dose-dependent depression by isoflurane, whereas MUT responses were dose-dependently enhanced across this range (fig. 6A). These observations were extended across a wide concentration range (fig. 6B) in independent experiments: at 6 mmol litre$^{-1}$, WT responses were depressed about five-fold while MUT conductances were potentiated to a similar degree and showed no tendency to saturate. To seek a mechanism for the divergent modulation, desensitization kinetics for the two isoforms were characterized. Neither WT or MUT receptors desensitized significantly ($P$>0.05, $n$=5–7) in response to a 3-min challenge with saturating GABA 2 mmol litre$^{-1}$ in the absence or in the presence of isoflurane 6 mmol litre$^{-1}$.

At concentrations in the clinical range (0.1–0.7 mmol litre$^{-1}$) isoflurane weakly (<2-fold) upregulated currents through both receptor isoforms. Low affinity responses to the anaesthetic were qualitatively divergent for WT and MUT channels, which were both demonstrably non-desensitizing. A point mutation in the receptor protein clearly impinges on the anaesthetic pharmacology in the invariant lipid environment of the oocyte membrane. This reinforces suggestions that isoflurane interacts directly with channel forming proteins and highlights the putative involvement of the M2 channel domain, in anaesthetic recognition, by the ligand-gated receptor superfamily.[3]

**Key words**
Brain, GABA$_A$. Receptors, GABA. Anaesthetics volatile, isoflurane.

**Acknowledgement**

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## Action of isoflurane at GABA$_A$ receptors: effect of intracellular calcium and diffusible cytoplasmic messengers

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The GABA$_A$ receptor is a sensitive target for anaesthetics,[1] the channel proteins may be modulated directly[1] or as a consequence of changes in cytoplasmic messengers[2] or free intracellular calcium ([Ca$^{2+}$]$_i$).[3]

Primary cultures of rat cortex were grown in neurobasal media with B27 serum replacement (Sigma). Two patch conformations were used—non-invasive amphoteracin perforated recording ($n$=6) was compared with whole-cell patch clamp which facilitates loss of diffusible macromolecules from the cytoplasm.

Potassium gluconate-based intracellular solutions which contained BAPTA 12 mmol litre$^{-1}$ ($n$=6) or EGTA 1.25 mmol litre$^{-1}$ ($n$=5) calculated to buffer [Ca$^{2+}$]$_i$ to 5 nmol litre$^{-1}$, or 330 nmol litre$^{-1}$, respectively. GABA concentration response curves were fit to a three-term logistic equation before, during and after

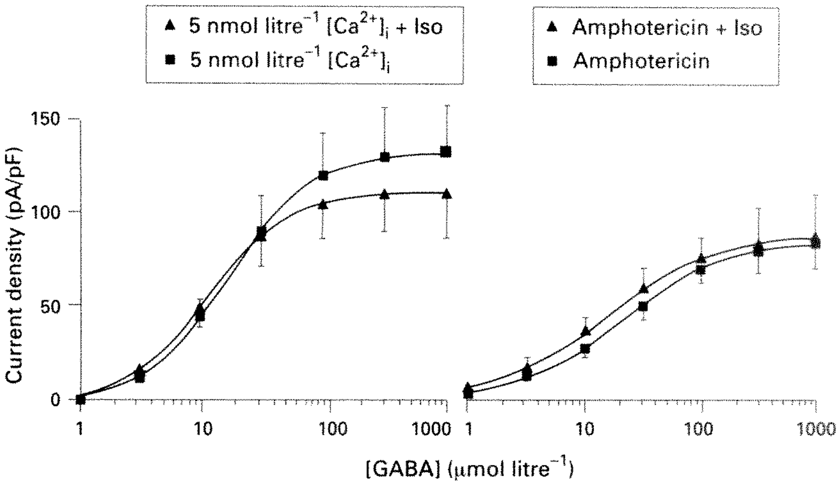

*Figure 7* GABA concentration response curves and the effect of isoflurane (means (SEM)).

the application of isoflurane 320 μmol litre$^{-1}$ (the control curve being taken as the mean of the pre- and post-isoflurane response).

Results were normalized for cellular capacitance to compensate for cell size. The effect of isoflurane on individual cells was analysed by paired *t*-test, a one-tailed test being used for the predicted reduction in $EC_{20}$. Comparison of isoflurane effect between groups was made by one-way analysis of variance.

Figure 7 shows the effect of isoflurane on the cells in the perforated patch group and whole cell ([Ca$^{2+}$]$_i$ 5 nmol litre$^{-1}$) group. In acute experiments, the response to high concentrations of GABA was equally depressed by isoflurane in the whole cell and perforated patch conformation. In all conformations isoflurane induced a significant ($P<0.05$) reduction of the GABA $EC_{20}$. No significant difference ($P>0.05$) in potency ratio or maximal GABA response depression was seen between groups.

Isoflurane enhanced the affinity of GABA for its receptor and upregulated chloride currents at subsaturating agonist concentrations regardless of the intracellular milieu. Diffusible messengers do not regulate anaesthetic-induced modulation or desensitization at high GABA concentrations.

**Key words**
Brain, $GABA_A$. Receptors, GABA. Intracellular messengers. Anaesthetics volatile, isoflurane.

### Acknowledgement

Supported by the Association of Anaesthetists of Great Britain and Ireland.

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## Effects of NMDA antagonists and thiopentone on glutamate release from rat cerebrocortical slices

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There are several reports to suggest that i.v. anaesthetic agents interfere with the release of glutamate.[1 2] In a previous study we have shown that thiopentone and ketamine did not affect the re-uptake of this neurotransmitter.[3] We have therefore examined the effects of these agents on K$^+$ (46 nmol litre$^{-1}$) evoked release of glutamate from rat cerebrocortical slices.

Cerebrocortical slices 350 μm thick were prepared from female Wistar rats (200–250 g). Immediately after suspension in oxygenated (95% oxygen, 5% carbon dioxide) Krebs buffer pH 7.4, the slices were pipetted into a perfusion chamber constructed from the barrel of a 2-ml syringe. Glass wool was packed into the needle end to retain the slices and a flow diffuser inserted. Slices were perfused at 1 ml min$^{-1}$ in Krebs buffer for 1 h, after which 2-ml fractions were collected for 6 min, before a 2 min pulse of 46 mmol litre$^{-1}$ K$^+$ ($S_1$). Slices were perfused for a further 30 min, before the second pulse of K$^+$ ($S_2$). Ketamine, thiopentone 3–330 μmol litre$^{-1}$ and MK-801 1 μmol litre$^{-1}$, used as an internal positive control were applied for 30 min between $S_1$ and $S_2$. Glutamate concentrations were measured fluorimetrically based on the conversion of NADP$^+$ to NADPH by glutamate dehydrogenase. From the area under the stimulation profiles, the $S_2/S_1$ ratios and the percentage inhibitions were calculated. Data are mean (SEM) for $n=5$–8, and were analysed by Wilcoxon rank sum test.

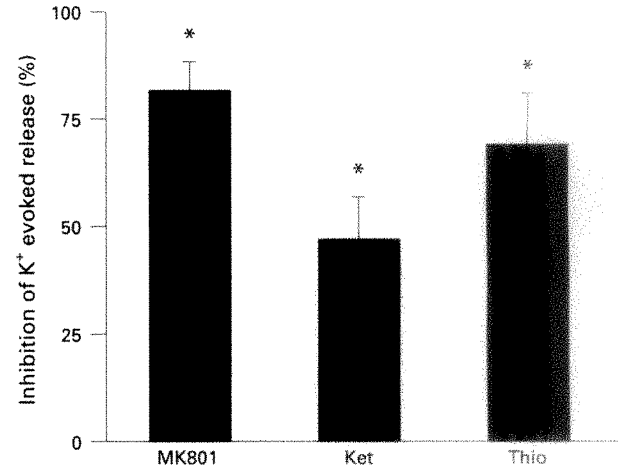

*Figure 8* MK-801 1 μmol litre$^{-1}$, ketamine (Ket, 30 μmol litre$^{-1}$) and thiopentone (Thio, 30 μmol litre$^{-1}$) inhibit K$^+$ evoked glutamate release. $^*P<0.05$ compared with paired control.

Thiopentone and ketamine produced a dose-dependent inhibition of K$^+$-evoked glutamate release, with an estimated $IC_{50}$ of around 10 μmol litre$^{-1}$. MK-801 at 1 μmol litre$^{-1}$ also inhibited release (fig. 8).

These data confirmed the inhibitory effects of MK-801 and ketamine on glutamate release, that presumably resulted from NMDA receptor block. The site(s) of action for thiopentone will require further investigation.

**Key words**
Rat brain. Brain, metabolism, Anaesthetics i.v.

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## Target-controlled infusion of Org 21465, a new anaesthetic steroid

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Org 21465 is a water-soluble steroidal i.v. anaesthetic. In a previous study, infusion of 1.0–1.8 mg $kg^{-1}$ over 1 min induced anaesthesia in volunteers.[1]

Six healthy male volunteers aged 22–30 yr weighing 63–82 kg each received a 45-min infusion of Org 21465. The rate of infusion was computer-controlled by a pharmacokinetic model driven infusion programme using pharmacokinetic data from the previous study.[1] The infusion programme was set to give three consecutive 15-min periods with stable plasma concentrations of 0.5, 1 and 2 $\mu g\ ml^{-1}$.

After cannulation, subjects rested quietly and received supplementary oxygen by a nasal cannula. Direct arterial pressure, oxygen saturation, ECG, bio-impedance cardiac output, and EEG (high resolution, 7 channels) were monitored continuously. Arterial samples were collected for pharmacokinetic analysis. Org 21465 was infused through a central venous catheter passed from the antecubital fossa.

All subjects were sedated at the lowest target concentration and anaesthetized at the highest. Measured concentrations of Org 21465 were stable during the three 15-min 'steps' and the concentration data from individual subjects were tightly grouped. Measured concentrations were higher than predicted (fig. 9). Heart rate increased progressively at the highest drug concentration. Systolic arterial pressure decreased slightly. All subjects developed excitatory movements, EEG showed dose-related depression without excitation.

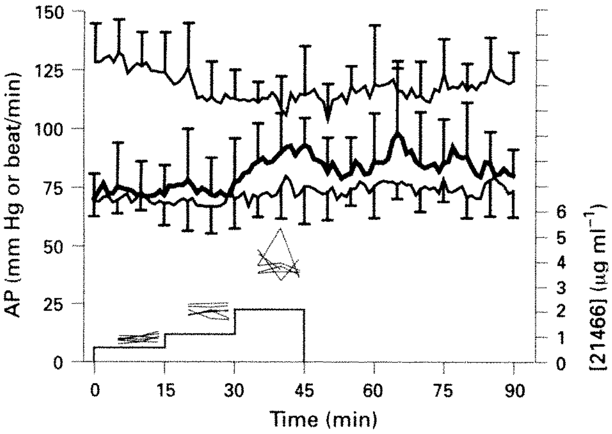

*Figure 9* Systolic and diastolic arterial pressure and heart rate (middle line), mean (SD), before during and after a computer controlled infusion of Org 21465. Measured plasma concentrations in individual patients (thin lines) were higher than predicted (thick line).

Infusion of Org 21465 can produce sedation or anaesthesia. Excitation appears to be dose related, greatest at higher plasma drug concentrations and is probably of subcortical origin. The pharmacokinetics of Org 21465 require further analysis.

**Key words**
Anaesthetics, i.v. Hormones steroids.

**Acknowledgements**

Supported by Organon Teknika, Dr Sneyd has been paid for advice.

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## Can enoximone trigger malignant hyperthermia?

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It has been suggested that enoximone may trigger malignant hyperthermia (MH), and should be avoided in susceptible (MHS) individuals.[1 2] We therefore studied the effect of enoximone on isolated muscle strips from MHS patients and the effect on subsequent *in vitro* contracture testing (IVCT).

We studied 21 patients who were referred for MH screening (11 MHS, 10 normal). Muscle biopsy and IVCT was performed according to the European MH Group protocol.[3] Halothane contracture tests were repeated on additional muscle strips that had been exposed to enoximone (preservative free) 10 $\mu mol\ litre^{-1}$ for 10 min. All tests were performed within 5 h of biopsy. We observed any changes in tension of the strips after enoximone exposure and whether enoximone altered the contracture response to halothane. We compared changes in maximum tension during IVCT with/without enoximone using Wilcoxon's matched pairs signed rank test.

There was no increase in tension in MHS or normal muscle after exposure to enoximone alone. Neither did any normal muscle strip develop a contracture when halothane was added in the presence of enoximone. Enoximone did not significantly affect the maximum response to halothane in MHS muscle ($P=0.56$, power >80% to detect a difference of ≥1 g) (fig. 10).

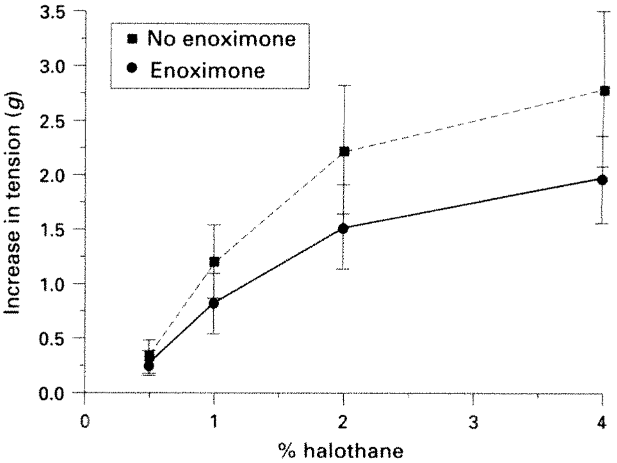

*Figure 10* Effect of enoximone on halothane-induced contracture of muscle from MHS patients (mean (SEM), $n=11$).

The concentration of enoximone used in this study exceeds the maximum plasma concentration achieved therapeutically. It is unlikely that therapeutic concentrations of enoximone will trigger MH or increase response to volatile anaesthetics.

**Key words**
Complications malignant hyperthermia. Anaesthetics volatile, enoximone.

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### Cardiovascular changes following administration of remifentanil in combination with either propofol or isoflurane

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The traditional method of presenting cardiovascular data has been to use repeat measures ANOVA for changes with time within a group and multiple individual tests to compare between groups at time points. We present the use of the mean absolute deviation (MAD) score as a measure of cardiovascular variability. Similar techniques have been used to assess variability of infusion systems.[1]

The present data are part of a multicentre study designed to compare responses following remifentanil as part of an inhalation technique with isoflurane, or as part of a total i.v. technique with propofol.

A total of 233 ASA I or II adult patients undergoing surgery anticipated to last at least 30 min were recruited. The patients were unpremedicated and at commencement of anaesthesia received a pre-induction bolus of remifentanil 1 $\mu g\ kg^{-1}$ together with an infusion commenced at 0.5 $\mu g\ kg^{-1}\ min^{-1}$. Anaesthesia was induced with propofol and after neuromuscular block the trachea was intubated. Patients were randomized to receive (a) TIVA, with propofol 9 $mg\ kg^{-1}\ h^{-1}$ reduced to 6 $mg\ kg^{-1}\ h^{-1}$ after 10 min or (b) isoflurane to an end-tidal concentration of 0.6%. The remifentanil infusion was reduced to 0.25 $\mu g\ kg^{-1}\ min^{-1}$ 5 min after intubation. All patients were ventilated to normocapnia with oxygen-enriched air. Non-invasive arterial pressure and pulse were recorded before induction, at loss of consciousness, before and after intubation, before and after skin incision and at 5-min intervals thereafter.

Systolic arterial pressures (SAP) were compared between groups (Student's *t*-test). Variability of systolic spherical pressure in each patient was represented by the MAD score. The mean SAP was calculated for each patient and the absolute difference of each recorded SAP from this mean was determined. The MAD score for each patient was the mean of these differences.

There was no statistical difference between the groups with respect to age, sex or weight. The mean induction dose of propofol was 1.44 (0.64) for TIVA *vs* 1.46 (0.58) $mg\ kg^{-1}$ for isoflurane. The cardiovascular responses to intubation and skin incision are shown in table 5.

*Table 5* Mean systolic arterial pressures (SD). $^*P<0.05$ between groups

| Systolic arterial pressure (mm Hg) | Isoflurane | Propofol |
|---|---|---|
| Before induction | 133 (17) | 134 (17) |
| After induction | 122 (23) | 125 (23) |
| 5 min after intubation | 95 (19) | 100 (17) |
| 5 min after skin incision | 97 (14) | 101 (17)* |
| MAD score, mean (SEM) | 9.0 (0.4) | 8.9 (0.4) |

When remifentanil was used with propofol or isoflurane there was a reduction in systolic arterial pressure with time in both groups. There was no significant difference between the groups in cardiovascular responses to induction or intubation; however, there was a statistical difference after skin incision. There were no significant differences between the groups in cardiovascular variability as calculated by MAD scores.

**Key words**
Arterial pressure. Anaesthesia, general.

**Acknowledgements**

The study was supported by Glaxo Wellcome. We acknowledge access to the data from other centres.

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### Recovery after induction and maintenance of anaesthesia with sevoflurane/oxygen in adult outpatients. A comparison with propofol/sevoflurane/oxygen

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The pharmacokinetic profile of sevoflurane parallels that of propofol.[1] The drug possesses a pleasant smell with little or no respiratory tract irritation. We have used sevoflurane alone for induction and maintenance of anaesthesia and compared patient recovery characteristics with those when propofol was used for induction and sevoflurane for maintenance.

After local Ethics Committee approval, 40 adult patients (ASA I and II), aged 18–60 yr, presenting for body surface surgery on a day-care basis were studied. No premedication was used. Patients were allocated randomly to receive either sevoflurane for both induction (using a vital capacity breath technique) and maintenance of anaesthesia (group 1; $n=20$) or propofol for induction followed by sevoflurane for maintenance (group 2; $n=20$). In group 1, inspired sevoflurane was administered in oxygen-enriched air ($F_{IO_2}=0.4$) at an inspired concentration of 8%. Loss of the eyelash reflex was taken as the end point of induction. The time taken and the number of breaths to this point was noted. In group 2, propofol was administered in a dose sufficient to abolish the eyelash reflex and the time to achieve this was noted. After induction, patients in both groups breathed oxygen and air ($F_{IO_2}=0.4$) and sevoflurane (2–3% end-tidal) through a laryngeal mask using a standard breathing system with a fresh gas flow of 5 litre $min^{-1}$. Analgesia, when required, was provided by non-steroidal anti-inflammatory drugs (NSAID) or appropriate local blocks. The duration of anaesthesia was noted. Recovery was assessed by the times to eye-opening on command, to giving correct first name and date of birth and to sitting up unaided. Statistical analyses of the data were performed using ANOVA or Student's *t*-testing; a *P* value of <0.05 was significant.

The mean times taken for induction of anaesthesia and end-tidal concentrations of sevoflurane were similar in both groups. Patients in group 1 opened their eyes, were able to state their first name and date of birth and sat up sooner than those in group 2 (table 6).

*Table 6* Induction times, duration of anaesthesia and recovery characteristics. Data are mean (SD). $^*P=0.0001$; $^{**}P=0.0006$

| | Group 1 | Group 2 |
|---|---|---|
| Induction time (s) | 44 (26) | 40 (8) |
| Eye opening (min) | 6.3 (2.0)* | 9.5 (2.70) |
| First name (min) | 6.5 (2.0)* | 9.8 (2.7) |
| Date of birth (min) | 6.8 (1.9)* | 9.9 (2.6) |
| Sit-up (min) | 7.4 (2.1)** | 10.9 (3.7) |
| $F'_E$ sevofluane (%) | 2.8 (0.4) | 2.8 (0.3) |
| Duration of anaesthesia (min) | 15.8 (8.0) | 15.3 (10.1) |
| No. of breaths | 6.1 (1.2) | – |

We concluded that sevoflurane was an acceptable alternative to propofol for induction of anaesthesia and provides excellent recovery when used as a single agent.

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**Key words**
Anaesthetics i.v., propofol. Anaesthetics, volatile, sevoflurane. Anaesthesia, outpatient.

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### Effect site modelling of combined fentanyl bolus and alfentanil infusion

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We have used computer modelling to investigate the potential for saving an expensive infused narcotic, alfentanil, by pre-treatment with a bolus of a longer-acting and cheaper drug, fentanyl. The effect compartment kinetics of fentanyl and alfentanil have been estimated from the hysteresis between plasma concentration and the 95% spectral edge of the EEG.[1] MAC reduction of enflurane in dogs suggests that fentanyl is 10 times more potent than alfentanil.[2] Simulations of effect site concentrations were computed in a three-compartment model using STANPUMP (version 13 June 1995, available from URL:http://pkpd.icon.palo-alto.med.va.gov).

The predicted effect site concentration over 5 h of a fentanyl bolus of 10 µg $kg^{-1}$ given to a 70 kg, 190 cm male was calculated and converted to the equivalent alfentanil effect site concentration using a potency ratio of 10:1. The difference between the equivalent alfentanil effect site concentration and an arbitrary target effect site concentration of 150 ng $ml^{-1}$ may be called the "effect site deficit". Three alfentanil infusion schemes were simulated to fill this theoretical effect site deficit: .25 µg $kg^{-1}$ $h^{-1}$ for 3 h; :50 µg $kg^{-1}$ $h^{-1}$ for 45 min then 25 µg $kg^{-1}$ $h^{-1}$ for 2 h 15 min and a target controlled infusion (TCI) for 3 h (fig. 11).

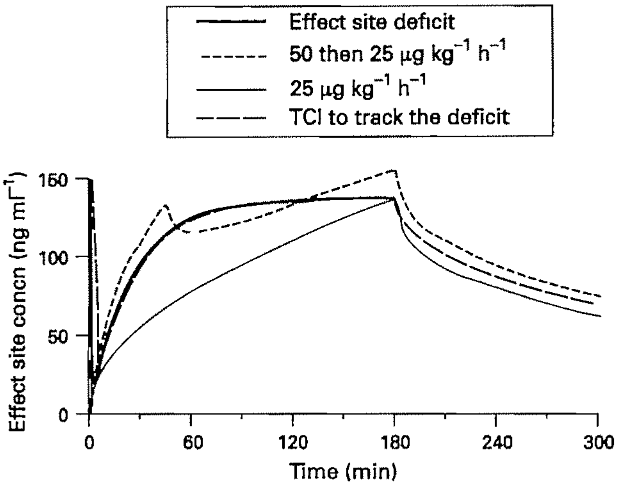

*Figure 11* Effect site deficit and three different alfentanil infusion schemes to fill it.

The quantities of alfentanil used by these infusion schemes were: 25 µg $kg^{-1}$ $h^{-1}$, 5.3 mg; :50 then 25 µg $kg^{-1}$ $h^{-1}$, 6.6 mg and TCI to fill the deficit 6.3 mg. If no fentanyl had been given, 7.3 mg of alfentanil would have been needed to achieve a steady-effect site concentration of 150 ng $ml^{-1}$.

For fentanyl and alfentanil with a potency ratio of 10:1 there was minimal saving in drug usage, and a simple two-step infusion approximated the target-controlled infusion. Perhaps rapid effect site kinetics and expense will make remifentanil more suitable for an effect site target controlled or manual infusion to top-up a long-acting opioid given by bolus or infusion. Potential benefits include intense and cost effective intraoperative narcosis with rapid offset and residual analgesia during recovery.

**Key words**
Model, effect site. Model, computer simulation.

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## More about predicting arterial $P\text{CO}_2$ from end-tidal

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When ventilator rate is halved from 20 to 10 $min^{-1}$, and tidal volume thereby doubled, the resultant change in end-tidal $P\text{CO}_2$ at 20 $min^{-1}$.[1 2] For this study we wanted to see if the estimate of arterial $P\text{CO}_2$ at the lower rate of 10 $min^{-1}$ could be improved, by changing ventilatory rate to 20 $min^{-1}$, simultaneously halving tidal volume.

We studied 24 patients, 20 of them male, undergoing routine cardiac surgery; their mean age was 60 (range 38–73) yr. They were ventilated with enflurane in air/oxygen via a Servo ventilator 900C at 10 $min^{-1}$. Inspiratory and pause time were 25% and 10% of cycle throughout. End-tidal $P\text{CO}_2$ was measured with a Siemens 930 capnograph, calibrated against the blood-gas analyser.[3] At steady state, end-tidal $P\text{CO}_2$ was noted, and then during an expiration the rate was changed to 20 $min^{-1}$, simultaneously halving tidal volume. End-tidal $P\text{CO}_2$ was noted for the first five breaths at the new rate.

The resultant change in end-tidal $P\text{CO}_2$ ranged from −0.4 to 0.1 kPa (in the previous study it ranged from −0.3 to 0.4). However, there was no relationship between the change in end-tidal $P\text{CO}_2$ and the arterial to end-tidal $P\text{CO}_2$ difference at 10 $min^{-1}$ ($r=-0.07$); in the previous study, those patients with the greatest arterial to end-tidal $P\text{CO}_2$ difference showed the greatest increase in end-tidal $P\text{CO}_2$ ($r=0.61$). This method therefore seems unpromising as a basis for refining the end-tidal-based estimate of $Pa_{\text{CO}_2}$ at low ventilatory rates.

The reason for this lack of relationship, and the failure to discriminate between patients with good and bad function, was unclear. Sudden changes in ventilator setting appear to have an asymmetrical effect on $\dot{V}/\dot{Q}$ relationships, depending on whether tidal volume is increased or decreased. It is possible that different functional residual capacities or compliances at the two settings may play a role.

**Key words**
Monitoring, arterial pressure. Partial pressure, arterial-end-tidal. Ventilation.

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## Antibody microprobe studies of immunoreactive galanin release in the spinal cord of the neuropathic rat

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After peripheral nerve injury dramatic changes are seen in neuropeptide synthesis in the dorsal root ganglia,[1] with significant increases in galanin and neuropeptide Y mRNA and a decrease in both calcitonin gene-related peptide and substance P mRNA.[2] The aim of this study was to investigate changes in central galanin release after peripheral nerve injury. Although the significance of galanin up-regulation is unknown, it has been postulated to play an inhibitory role in dorsal horn transmission.

Under sodium pentobarbitone anaesthesia, four 4/0 chromic gut ligatures were placed loosely around the right sciatic nerve of male Wistar rats to produce a chronic constriction injury.[3] The International Association for the Study of Pain guidelines for the care of experimental animals were followed.

At 10–14 days after ligature placement, the lumbar spinal cords of urethane-anaesthetized rats ($n=30$) were exposed. Using a micromanipulator, microprobes bearing immobilized antibodies to galanin were inserted into the dorsal spinal cord to a depth of 2.25 mm. After removal from the spinal cord and incubation in $^{125}$I-labelled galanin, autoradiographs of each microprobe tip were analysed using an image analysis system. *In vitro* microprobe images for each experiment were also analysed and normal rats were used as controls. binding of endogenous galanin results in deficits in binding of $^{125}$I-labelled galanin. Mean image analysis of defined groups of microprobes were compared, at 30-µs intervals, and the differences between specified groups were assigned statistical significance using Student's *t*-test.

In normal animals, there was a fairly extensive presence of immunoreactive-galanin throughout the dorsal horn, with a peak in the superficial dorsal horn. In the neuropathic rats there was a significantly greater peak of immunoreactive-galanin release in the superficial dorsal horn ($P<0.05$). As there is significant up-regulation of galanin synthesis in small to medium sized dorsal root ganglia cells, the likely source of this new zone of central galanin release is from primary afferent fibres, affected by the peripheral nerve injury. Since this increased release occurred spontaneously, and there is evidence for spontaneous pain in this model, the two may be linked.

**Key words**
Pain, neuropathic. Model, rat. Neuropeptides.

**Acknowledgement**

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## Oscillations in arterial saturation: implications for the measurement of cerebral blood flow with near infrared spectroscopy

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Near infrared spectroscopy (NIRS) is a non-invasive technique to determine cerebral blood flow using oxyhaemoglobin as a tracer.[1] It requires an arterial saturation swing which begins with a stable baseline desaturation. As mild arterial hypoxaemia is induced, oscillations in both arterial saturation and NIRS signals occur. These oscillations occur at the respiratory frequency suggesting a respiratory origin.[2] When arterial saturation oscillates, determining the point at which tracer input occurs becomes difficult, leading to errors in the measurement of flow.

We have developed a two-compartment computer model to examine the effects of changes in cardiorespiratory variables on arterial saturation during a simulated measurement of cerebral blood flow. One compartment represents dead space in which only gas mixing occurs, the other represents alveoli in which both mixing and gas exchange occurs.

During the desaturation phase alveolar oxygen concentration starts at normal values. During quiet respiration it exhibits small oscillations and this produces small changes in arterial saturation owing to the flat nature of the oxygen dissociation curve at this point. However, as the alveolar oxygen concentration declines, the working point on the oxygen dissociation curve moves on to progressively steeper parts of the curve. The consequence of this increasing gradient is that the small oscillations in alveolar oxygen concentration produce progressively larger oscillations in arterial saturation as the mean alveolar oxygen concentration declines.

The model confirms that oscillations in arterial saturation universally occur at respiratory frequency. As the arterial saturation decreases the magnitude of these oscillations increases, the magnitude of the oscillations in alveolar oxygen concentration are relatively constant. The interaction between minute, alveolar and tidal volumes on the magnitude of the oscillation is shown in figure 12.

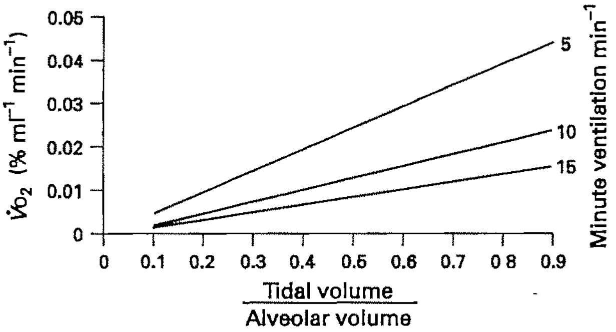

*Figure 12* Interactions between alveolar, minute and tidal volumes on the magnitude of arterial oscillation at a mean saturation of 90%

The model predicts circumstances where the oxyhaemoglobin technique will be impractical and allows optimization of respiratory parameters to enhance measurement of cerebral blood flow.

**Key words**
Brain, metabolism. Brain, blood flow. Measurement techniques, near infrared spectroscopy.

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## Performance of vaporizers in circle systems

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It is generally considered that vaporizers in circuit (VIC) are unsuitable for use with controlled ventilation (IPPV) and this is supported by a number of disasters that have followed the use of this technique. In a completely closed system with VIC, the inspired concentration of agent may rise to dangerous levels, owing to continual recirculation through the vaporizer We have conducted bench tests that confirm this is the case. However, computer simulation (using NARKUP) shows if the fresh gas flow (FGF) is increased above basal, and gas is lost from the system, the increase in concentration of agent is reduced and stabilizes at a level dependent upon the FGF.

This work suggested that VIC can be safely used with IPPV (provided agent monitoring is used) without adverse effects. We studied 20 patients, ASA I-II, having routine major orthopaedic surgery. Anaesthesia was induced with propofol and neuromuscular blockade achieved with vecuronium before intubation. In theatre, patients were attached to a Scania circle system with a Komesaroff vaporizer mounted in the inspiratory limb and ventilated using a Nuffield Penlon ventilator. Inspired and expired isoflurane and carbon dioxide concentrations were measured using a calibrated Datex Ultima analyser. Minute ventilation was adjusted to maintain an end tidal carbon dioxide of 4.0–4 5 kPa. The vaporizer settings were initially between 1 and 1.5 which gave an adequate inspired concentration of isoflurane in the circuit. Patients received either 1, 2 or 3 litre FGF.

In no case was the inspired anaesthetic concentration uncontrollable. After the first 10 min in theatre, the inspired concentration of isoflurane was stable (fig. 13).

At the lowest FGF used, the concentration of isoflurane tended to increase initially and in the majority of the patients required reduction of the vaporizer setting, after which no further adjustments were necessary. This effect was seen to a lesser degree at the 2- and 3-litre flow rates. We have shown that vaporizers can be

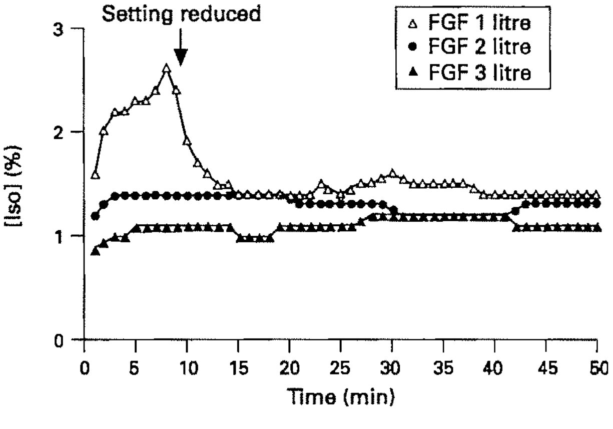

*Figure 13* Inspired isoflurane concentrations for three patients anaesthetized using VIC with three fresh gas flow rates (FGF).

used reliably and safely in the circle system. The stability of the anaesthetic concentration is conferred by controlled leakage from the system.

**Key words**
Circle systems. Vaporizers. Ventilation, intermittent positive-pressure.

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## Sequential veno-venous haemofiltration in the treatment of multisystem organ failure

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It has been suggested that haemofiltration has the potential benefit of removing inflammatory mediators and hence improving survival in multisystem organ failure.[1] The aim of this retrospective study was to evaluate the effects of sequential veno-venous haemofiltration (SVVH) on morbidity and mortality, when used as an early, elective treatment in critical illness to prevent the onset or progress of multisystem organ failure.

Fifteen critically ill patients with normal renal function (8 male, 7 female; age: median (m)=45, range (r)=16–65 yr) had undergone elective SVVH during an 18-month period. We compared survivors and non-survivors by their age, admission Apache II scores, predicted mortality, multiple organ dysfunction scores (MODS)[2] and haemofiltration characteristics. All patients received routine intensive care management, and the haemofiltration was started within 48 h of admission to the intensive care unit. For statistical analysis, Mann-Whitney and Fisher's exact tests were used.

Eight patients survived and seven died. There was no significant difference in age between the two groups (survivors: m=49, r=16–65; non-survivors: m=45, r=30–65). Apache II scores were higher in survivors (m=18, r=10–21) than non-survivors (m=14, r=7–20) as was predicted mortality (m=22, r=13–35% in survivors and m=11, r=7–20% in non-survivors). MODS before the onset of SVVH treatment was higher in non-survivors (m=7, r=4–12) than in survivors (m=5, r=0–8). None of these differences achieved statistical significance. All patients received daily SVVH up to a maximum of six treatments. There was no difference in the average total volume exchange during SVVH between survivors and non-survivors. The total fluid deficit during the course of the SVVH treatments was significantly higher in non-survivors (extracted fluid in litres: survivors: m=2.5, r=0–8; non-survivors: m=7, r=5–10; $P$=0.01). None of the survivors developed renal impairment, but five non-survivors subsequently developed acute renal failure. Heparin and epoprostenol sodium were used for anticoagulation during the treatments and we could not find any difference between their effects on physiological factors.

**Key words**
Blood, haemofiltration. Complications, multisystem organ failure.

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## Comparison of two wrapping systems for heat retention during anaesthesia

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Hypothermia can complicate anaesthesia. The use of active and passive warming methods should transmit an adequate amount of heat to maintain body temperature. The choice of passive methods includes body wraps some of which may prevent evaporative and convective heat loss, such as plastic bag, and others with reflective properties which could protect against radiation heat loss. It was hypothesized that, during prolonged major abdominal surgery, a plastic bag would be as effective in preventing heat loss as the more complex wraps incorporating reflective surfaces.

Forty patients presenting for hepatobiliary surgery were studied after informed consent. Two systems were used at random for heat retention: group 1 wore the Thermadrape garment (Vital Signs Ltd, Brighton), and group 2, large, transparent, thin plastic bags on the limbs and head. Active conduction of heat was standardized using a warm air mattress and blood warmers. An ambient theatre temperature of more than 21 °C was maintained. A nasopharyngeal probe measured core temperature and four peripheral skin temperature probes were used to calculate the mean skin temperature.[1] Measurements were taken every 15 min during surgery and the body heat calculated using the patient's weight. A standardized anaesthetic technique was used: induction with thiopentone and fentanyl, and vecuronium for neuromuscular block. After tracheal intubation, anaesthesia was maintained with oxygen, nitrous oxide and isoflurane in appropriate concentrations using intermittent ventilation of the lungs, through a heat and moisture exchanger. Additional analgesia was provided either with i.v. fentanyl or a thoracic extradural infusion of fentanyl and bupivacaine.

The two groups were similar with respect to age, weight, duration of operation, surgery performed, blood loss and anaesthetic technique. The mean core temperature increased by 1.5 °C (from 35.8 to 37.3 °C) in group 1 and by 1.4 °C (from 35.8 to 37.2 °C) in group 2. When core temperature increased above 37.5 °C active heating was stopped and cooling commenced. This occurred in two patients in each group. A mixed model analysis of variance was used to compare the relationship between heat intake and the time course of anaesthesia between the two groups. Both groups gained heat at about 50 kJ $h^{-1}$ for the first 3 h of surgery but after this heat gain continued in group 2 but not group 1.

Both systems of wraps for heat retention during surgery were effective in preventing heat loss and when combined with other methods produced hyperthermia. At the higher body temperatures achieved after 3 h of surgery, a change in the heat dissipation mechanisms may have produced the differences in heat gain observed between the two wrapping systems.

**Key words**
Temperature, body. Anaesthesia. Equipment, warming devices.

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## Effect of a bolus dose of midazolam on the auditory evoked response in humans

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Although midazolam given as a bolus has been shown to suppress the amplitudes and extend the latencies of the late cortical (N1, P1, N2, P2) and cognitive (P300) auditory evoked responses (AER) it has little effect on the early cortical AER waves Pa and Nb.[1] This has to be reconciled with the claims that features of the early cortical AERs indicate loss of awareness[2] and midazolam produces hypnosis. As the patient falls asleep Nb latency lengthens. The 50% cut-off from a discrimant function analysis was 44.5 ms.

Nine patients, aged 24–49 yr, were studied. None was premedicated and midazolam was given as a bolus of 20 mg over 5 s. The times until the eyelash reflex was lost and the airway required support were recorded. The AER was elicited by 75 dB (above HL) clicks presented binaurally at a rate of 6 ps. The EEG from which the AER was derived was recorded from silver-silver chloride cup electrodes attached to the scalp using collodion glue at the vertex and inion. These electrode sites were used in preference to the usual forehead and mastoid site to ensure better recordings in the awake patient. Nb latency was measured when the patient was awake, after loss of eyelash reflex and after requirement for airway support. The AER waveforms were averaged over 1024 sweeps, where possible, but occasionally, because the time to lose these reflexes is uncontrolled a shorter number of sweeps were used.

The eyelash reflex was lost 1.78 (0.50) min (mean (SD)) after the midazolam bolus. Two of the patients did not require airway support in the 10 min allowed for the study. The time to airway support for the rest of the patients was 2.74 (1.26) min. The effect of midazolam on Nb latency recorded immediately after these events is shown in figure 14. Analysis of variance was used and when the Bonferroni adjustment, for multiple comparisons, was applied there were significant differences between Nb latency from awake to loss of eyelash ($P<0.001$) and awake to airway support required ($P=0.003$).

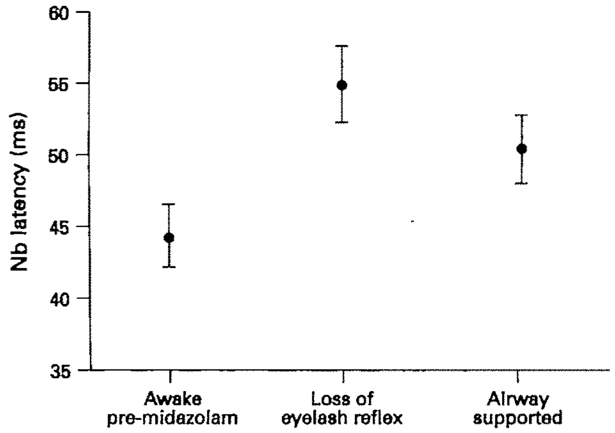

*Figure 14* Nb latency (means+95% CI) after a midazolam bolus.

We concluded that loss of consciousness induced by a midazolam bolus and indicated by loss of eyelash reflex and requirement for airway support was associated with a significant increase in Nb latency. This supports previous work[2] where a significantly increased Nb latency was related to loss of consciousness judged by loss of response to verbal command. However, we noted that even with the substantial dose of midazolam, which we gave, there was a variable effect in the time taken to these clinical end-points, if in fact they occurred at all. It is conceivable that smaller doses, combined with the variable response of the patient, may not necessarily achieve loss of consciousness. This would account for reports of intraoperative awareness, in particular the perception of auditory stimuli during anaesthetic regimes where benzodiazepines are used to suppress consciousness.[1]

**Key words**
Hypnotics benzodiazepines, midazolam. Monitoring, evoked potentials.

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## Changes in the early cortical auditory evoked response during hypothermia

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We have previously reported[1] the general effects of reduced core temperature on the auditory evoked response (AER). This study examines the association in more detail.

We recorded the AER in 42 adults during cardiopulmonary bypass (CPB) for elective coronary artery grafting. Premedication was diazepam 10–15 mg, morphine 10–15 mg and prochlorperazine 12.5 mg. Rarefaction clicks at 6.12 Hz and 65 dB loudness were played through moulded earpieces into both ears. The EEG was recorded between disposable silver-silver chloride electrodes (Medicotest P-00-S) on the mastoid processes and the vertex, using one mastoid electrode as ground. The resulting signal was digitized at 1 kHz and stored on computer disk. The AER was derived using the Northwick Park software, averaging 512 sweeps of 125-ms epochs of the EEG. Anaesthesia was induced with fentanyl 10 $\mu g\ kg^{-1}$, thiopentone 1 mg $kg^{-1}$ and pancuronium 12 mg. Anaesthesia was maintained with a further dose of fentanyl 5 $\mu g\ kg^{-1}$ before sternotomy and 0–1% isoflurane in the anaesthetic room then a propofol infusion 1–3 mg $kg^{-1}\ h^{-1}$. We recorded a baseline AER during stable conditions after, dissection of the internal mammary artery and then during cooling to 26 °C and subsequent rewarming to 37 °C on cardiopulmonary bypass at a mean arterial pressure of 40–70 mm Hg. The latency and amplitude of the Pa and Nb waves of the early cortical AER were measured for each 0.5 °C change in nasopharyngeal temperature (used as an approximation of brain temperature). Statistical analysis was done with one-way repeated measures ANOVA and *t*-testing, using SPSS for Windows and accepting significance at the 5% level.

The latencies of both the Nb and Pa waves increased with decreasing temperature between 37 °C and 28 °C ($r=-0.70$), the change from the baseline at 37 °C becoming statistically significant at 34.5 °C for both waves. The amplitude of the Pa wave was difficult to measure reliably. The amplitude of the Nb wave decreased with temperature, but the correlation was weak ($r=0.25$) as a result of wide variability in Nb amplitude at each temperature (table 7).

*Table 7* Mean latency (ms (SD)) of the early cortical waves of the AER

| | Temperature | | | | | |
|---|---|---|---|---|---|---|
| | 32 °C | 33 °C | 34 °C | 35 °C | 36 °C | 37 °C |
| Pa wave | 53.2 (11) | 46.4 (9) | 40.5 (9) | 38.2 (7) | 37.3 (6) | 34.5 (5) |
| Nb wave | 74.5 (11) | 67.3 (10) | 60.9 (9) | 58.6 (8) | 58.2 (8) | 55.5 (5) |

The effect of temperature on the AER is not significant until the patient is quite cold, so can probably be ignored during anaesthesia for most non-cardiac procedures.

**Key words**
Monitoring, evoked potentials. Temperature, effect. Measurement techniques, electrophysiology.

**Acknowledgement**

We thank Medelec for the loan of the AER monitor.

**Reference**

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## Effect of sevoflurane on the auditory evoked response, spectral edge and median frequency in humans

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The low blood-gas solubility of sevoflurane allows rapid changes in anaesthetic depth. In paralysed patients a reliable monitor of anaesthetic depth would be useful with this agent. This study compared the effect of sevoflurane on the auditory evoked response (AER) with the derived electroencephalogram (EEG) variables, that is median frequency (F50) and spectral edge (F95).

Twelve patients (aged 31–65 yr) gave informed consent to participate in a crossover study which had been approved by the Harrow Research Ethics Committee. After premedication with morphine 10 mg and atropine 0.4 mg, anaesthesia was induced by inhalation of sevoflurane in 66% nitrous oxide in oxygen. The patients were intubated after vecuronium 0.1 mg $kg^{-1}$ Subsequently, neuromuscular paralysis was maintained at a level of two twitches (TOF count) by vecuronium infusion. The EEG and AER were recorded throughout four consecutive 10-min periods. During each period, patients were maintained at end-tidal sevoflurane concentrations (0.5, 1 and 2%) in random order. In the fourth period, the concentration of the preceding period was repeated. This ensured that each concentration was preceded by every other concentration including itself an equal number of times. This design ensured that any "carryover" effect between periods would cancel out and allowed interaction between dose and time to be studied.

End-expiratory concentrations of sevoflurane, nitrous oxide and carbon dioxide were measured using a calibrated Datex Ultima gas analyser. Ventilation and fresh gas flow were adjusted to maintain an end-expiratory carbon dioxide between 4.5–5 kPa. For each concentration of sevoflurane, the AER and EEG analysis was carried out in the final 2.5 min of the 10-min period (when equilibrium was considered to have occurred). Analysis of variance was carried out on the $\log_{10}$ transformed data. A significant linear effect of dose was seen for all variables (see table 8).

*Table 8* Effect of sevoflurane concentration on AER and EEG variables (geometric means (95% confidence intervals))

| Variable | *P* value | 0.5% Sevo | 1% Sevo | 2% Sevo |
|---|---|---|---|---|
| Pa 1st | 0.01 | 35.5<br>(32.7–38.9) | 40.7<br>(37.2–44.7) | 42.4<br>(38.7–46.4) |
| Pa amp | <0.001 | 0.34<br>(0.25–0.46) | 0.19<br>(0.14–0.27) | 0.11<br>(0.08–0.15) |
| Nb 1st | 0.04 | 54.7<br>(50.1–59.7) | 59.6<br>(54.6–65.0) | 63.7<br>(58.3–69.5) |
| Nb amp | <0.001 | 0.26<br>(0.20–0.33) | 0.18<br>(0.14–0.23) | 0.11<br>(0.08–0.14) |
| F50 | <0.001 | 3.1<br>(2.6–3.7) | 2.1<br>(1.8–2.6) | 1.5<br>(1.3–1.8) |
| F95 | <0.001 | 15.8<br>(14.7–17.1) | 13.1<br>(12.1–14.1) | 7.9<br>(7.3–8.6) |

The results demonstrated that the AER and EEG derived variables had a linear relationship with the dose of sevoflurane, as previously demonstrated with desflurane.[1] Regression equations for each variable were calculated to give a percentage change for a 1MAC change in sevoflurane concentration. For example a 1MAC increase in sevoflurane concentration produces a 51% (95% confidence intervals 36–62) decrease in Pa amplitude and a 35% (29–40) decrease in F95. These percentage changes were similar to 1MAC percentage changes for desflurane where Pa amplitude decreased by 49% (40–56) and F95 decreased by 33% (25–41).

This confirms that analysis of AER and EEG variables continues to be a useful research tool in the search for a monitor for depth of anaesthesia.

**Key words**

Anaesthetics volatile, sevoflurane. Monitoring, evoked potentials.

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## Use of a photographic method to compare rigid laryngoscopy techniques

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The basis for a method to compare the relative efficiency of laryngoscope blades has been outlined.[1] This requires use of a standardized intubating position,[2] mouth closed around the blade, consistent technique, controlled displacement of the larynx, accurate photographic record of view of laynx,[3] and that the blade should be positioned below the epiglottis. (The latter allows reasonable comparisons between straight and curved blades.) This pilot study compares a Macintosh 3 blade with the narrow Sheila Anderson straight blade of equivalent length, in subjects who were not expected to be difficult laryngoscopies.

Ten subjects (ASA I–II) scheduled for tonsillectomy or nasal surgery were recruited. Patients at risk of oesophageal reflux or with a history of difficult intubation were excluded. Oral premedication was with diazepam 10 mg. After preoxygenation, anaesthesia was induced with midazolam (0.04 mg $kg^{-1}$), propofol (2 mg $kg^{-1}$) and vecuronium (0.15 mg $kg^{-1}$) and maintained with a standard propofol infusion plus hand ventilation with equal volumes of oxygen and nitrous oxide. When the train-of-four suppression was complete, alfentanil (15 $\mu g$ $kg^{-1}$) was given just before laryngoscopy. Photographic records were made of the view with each laryngoscope. The photographer used a fixed focal distance and moved to a position along the optimum eyeline till the cords were in sharp focus. (In each case view with the Macintosh blade was assessed before the straight blade.) When each view was recorded a simultaneous lateral photograph of the head and neck position was taken to check the position. All the patients were followed up at 4–6 h postoperatively.

A good record was considered to be one where the upper teeth or lip and posterior part of the laryngeal inlet or arytenoids were adjacent on the photographic image. In all the cases except one, good views of the larynx were obtained. In this case view with the Macintosh blade was satisfactory but poor control of the epiglottis did not allow a good view with the straight blade. Otherwise the view with each blade was comparable.

The maximum depth of laryngeal exposure measured in these subjects was 1.5 cm. In no case was all of the larynx visible on the image even though this was usually the case as far as the anaesthetist was concerned. As has been documented in earlier work, the photographic image is not the same as the composite perceived by the anaesthetist who scans the larynx by panning to determine how much of the larynx can be visualized.[3] This is a limitation of this method, but this "restricted window" effect may well be relevant only when the view is good and unimportant when little or no part of the larynx is visualized.

**Key words**

Larynx, laryngoscopy.

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## Development of a computer system for prediction of difficult laryngoscopy

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Failed intubation remains an important life-threatening event under anaesthesia. Currently, anaesthetists attempt to anticipate the degree of difficulty from the medical and anaesthetic history and relevant clinical examination by way of simple bedside tests.[1] The incidence of difficulty in intubation is said to be between 1.2% and 2.5%. Of these, 75% of the cases have been claimed to be predictable, though this figure also includes 12% of false positive predictions.[2] However, it is in the remaining 25%, that cannot be predicted preoperatively by the above conventional medical procedures, that present the anaesthetist with the greatest difficulty.

We developed a computer simulation to predict difficult intubation cases from historical patient data. The system was based on mathematical models of the laryngoscopy process.[3] Users of the system were able to select, position and orientate different blade types on a computer screen which showed a stylized cross-section of the airways. Blade movements which were responsible for tongue deformation were guided by pressing the mouse buttons. These movements were restricted, first, by the incisors and, second, by the tongue compressed between the blade and the inner boundaries of the lower jaw. Geometric constraints were made explicit either as imposed conditions that cannot be violated (for example, the point representing the tip of the incisors cannot penetrate the blade) or as monitored conditions whose violation was reported to the user (for example, when the tongue became maximally compressed). Measures relating to difficult intubation were calculated, and a simulated view of part of the vocal cords was drawn. This provided an intuitively simple way of grading the difficulty of laryngoscopy relative to the cord visualization. Simulation results such as charts and images were saved to files for later demonstration, analysis and clinical diagnosis.

Preliminary evaluation of the system has been carried out using patient histories and the subjective assessments of experienced anaesthetists, and the results are encouraging. A more comprehensive prospective systematic study, involving 20 patients is currently being undertaken .

**Key words**

Larynx, simulated laryngoscopy. Intubation, tracheal, complications. Model, computer simulation.

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## Inhibition of nitric oxide synthase antagonizes curare-induced tetanic fade

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Nitric oxide modulators have been shown to influence the contractility of directly stimulated muscle[1] and to affect spontaneous synaptic currents in the embryonic neuromuscular synapse.[2] To study the macroscopic effect of this class of drug we have investigated the actions of the nitric oxide synthase inhibitor, 7-nitroindazole, upon curare-induced fade in the rat hemidiaphragm.

Left hemidiaphragms of male Sprague-Dawley rats (280–320 g) were isolated and mounted in a bath of Krebs-Henseleit solution containing 0.5 µmol litre$^{-1}$ tubocurare at 32 °C perfused with 95% oxygen/5% carbon dioxide. Single 0.2-ms pulses of supramaximal voltage (5–8 V) were applied to the phrenic nerve and the resultant twitch responses transduced and recorded. Upon stabilization, tetani of 2-s duration were administered. One tetanus was applied, at 1-min intervals, at each of the following frequencies: 10, 20, 25, 30, 35, 40, 50 and 75 Hz The bathing solution was then replaced with one containing the study drug, and after a 30-min incubation period, the same pattern of tetani was repeated.

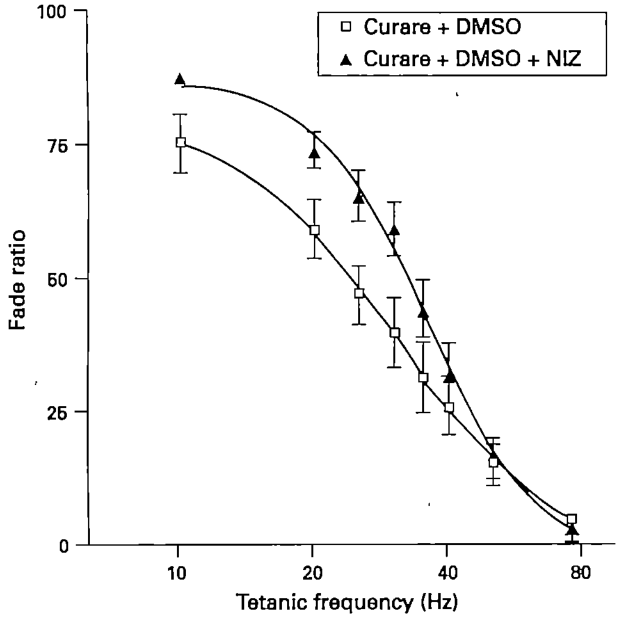

*Figure 15* Results. $n$=6 for both groups. The two groups are significantly different ($P$<0.01, ANOVA).

A curare solution 0.5 µmol litre$^{-1}$ with 7-nitroindazole 0.32 mmol litre$^{-1}$ plus 0.104% dimethyl sulphoxide solvent was compared with one without the 7-nitroindazole. The fade ratios at each frequency of their tetanic trains were measured and fitted to frequency response curves by non-linear regression using GraphPad Prism software. The two sets of results were compared by two-way ANOVA.

Mean (SEM) results for dimethyl sulphoxide with and without 7-nitroindazole are shown in figure 15.

The finding that 7-nitroindazole antagonizes curare-induced tetanic fade supports the belief that nitric oxide decreases quantal release in the neuromuscular junction.[2]

**Key words**

Muscle relaxants, nitric oxide. Neuromuscular junction. Model, rat.

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## Persistent pain of reflex sympathetic dystrophy

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The pain of reflex sympathetic dystrophy (RSD) or complex regional pain syndrome in the upper extremity has been traditionally treated with repeated stellate ganglion blocks (SGB) in expectation of providing increasing duration of pain relief to arrest the pain syndrome. There are few data regarding efficacy of SGB or supporting the notion that subsequent SGB will provide in increasing duration of pain relief.

We studied 25 consecutive patients with upper extremity RSD of greater than 12 months' duration who met five of nine criteria for the diagnosis of RSD: (1) diffuse burning pain of the hand, (2) relief of pain after SGB, (3) colour difference between hands, (4) allodynia/hyperpathia, (5) temperature difference between hands >1 °C, (6) oedema, (7) sudomotor symptoms, (8) decreased range of motion of hand or wrist, (9) trophic changes of the skin. Data were collected using a standardized history and physical examination. Data were reported as mean (SD) (range), or percentage.

Patient characteristics were: sex 36% M; 64% F; duration of pain: 52 (45) months (range 12–184); visual analogue pain score (0–10): 6.9 (2.5) (range 2–10). Mean number of SGB per patient was 17.7 (39) (range 9–200). Of the 24 patients who reported relief of pain after SGB, median pain relief was 40 h. Only one patient who had relief of pain after SGB reported an increasing duration of analgesia with subsequent SGB. Opioids were used by 88% of patients, with mean daily oral morphine equivalent dose of 37 (59) mg (range 5–240). Tricyclic antidepressants were used by 72%, and other antidepressants by 16%. Anticonvulsants were used by 12%. Twenty-four percent of the patients were currently undergoing hand therapy, although it had originally be prescribed for all

Our results and those of Veldman,[1] who used similar diagnostic criteria, revealed a subset of RSD patients whose pain was not cured despite aggressive and early SGB. These patients did not demonstrate an increasing duration of analgesia with subsequent blocks. Continuation of SGB appeared to be without justification. Hand therapy appeared to be too painful for most of these patients, so they refused to continue. For the majority of RSD patients refractory to SGB therapy, oral medications were helpful in providing analgesia.

**Key words**

Pain, pathological. Anaesthetic techniques, regional, stellate ganglion.

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## Nitrous oxide enhances the spread of spinal analgesia

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Systemic opioids enhance the spread of spinal analgesia produced by lignocaine.[1 2] Nevertheless, systemic opioids may be associated with undesirable effects. In the present study we investigate the effect of 50% nitrous oxide on the spread of spinal analgesia.

Forty patients undergoing transurethral prostatectomy under spinal anaesthesia were studied. In the operating room all patients received Ringer's lactate solution 500 ml and an $F_{IO_2}$ 0.35 via a Ventimask. Spinal anaesthesia was performed with the patient in the left lateral position. After local infiltration with 2% lignocaine, 5% hyperbaric lignocaine 100 mg (Xylocaine, Astra SG 1030-1035) was injected in the L3-4 interspace via a 25 gauge Whitacre needle, and the patient was placed in the lithotomy position. The level of spinal analgesia was established 20 min after spinal injection by means of a pressure feeler. Then patients received randomly either 50% nitrous oxide in oxygen (nitrous oxide group) or 50% nitrogen in oxygen (control group). The level of spinal analgesia was reassessed 10 min later under nitrous oxide or nitrogen inhalation. The nitrous oxide or nitrogen were discontinued, and the level of analgesia was reassessed 5 min after discontinuation. All assessments were done behind a screen by the same anaesthetist who was unaware whether nitrous oxide or nitrogen was administered. Results were analysed with unpaired Student's *t*-test.

Patient characteristics were similar in the two groups. One patient in the control group was excluded owing to a high level of spinal anaesthesia. Results are given in table 9.

*Table 9* Changes to the pressure feeler response in cm (mean (SD)) for each group (*$P<0.001$, **$P<0.01$, †$P=0.024$). In cols 1 and 3 time is compared with basal (20 min after block) and in col 2 time is compared with col 1

| Group | 10 min after $N_2O$ or $N_2$ inhalation | 5 min after $N_2O$ or $N_2$ discontin. | 35 min after spinal anaesthesia |
|---|---|---|---|
| $N_2O$ (n=20) | 1.56 (1.97)* | −3.52 (2.29)** | −2.20 (2.89)† |
| Control (n=19) | −3.14 (2.67)* | −1.46 (1.37)** | −4.53 (3.28)† |

These data suggested that inhalation of 50% nitrous oxide enhanced the spread of spinal analgesia. This effect subsided rapidly 5 min after nitrous oxide discontinuation, but still a significant difference was found compared with the control group.

**Key words**
Anaesthetic techniques, spinal. Anaesthetics gases, nitrous oxide.

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## Mid-tarsal block for surgery on the forefoot; what is the optimal local anaesthetic mixture?

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The mid-tarsal block allows the performance of surgery on the foot while the patient is awake and also provides analgesia for the postoperative period.[1] This block is performed distally where the nerve fibres are smaller and therefore are blocked quickly by local anaesthetics so delay of onset is not usually a clinical problem. When the block recedes, however, the patient can experience severe pain and half require parenteral opioids.[2] If a local anaesthetic mixture could provide prolonged analgesia this would improve the patient's comfort and ability to perform physiotherapy. This was investigated by a prospective, randomized double-blind trial.

Sixty-two patients scheduled for elective surgery of the forefoot were randomized into four groups depending on the local anaesthetic mixture used to provide the nerve block. Groups LBA and LB consisted of a 50:50 mixture of 2% lignocaine and 0.5% bupivacaine with or without adrenaline 1/200 000 respectively. Groups BA and B consisted of 0.5% bupivacaine with or without adrenaline 1/200 000 respectively. Patients received increments of midazolam 1–2 mg i.v. as required for sedation. Non-invasive blood pressure, pulse oximetry and electrocardiogram were monitored. The foot was exsanguinated and an ankle tourniquet inflated to 250 mm Hg. When surgery was completed patients were prescribed analgesia as oral coproxamol two tablets, 4 hourly (maximum 8 in 24 h) or i.m. morphine 0.15 mg $kg^{-1}$ 3-hourly. Time to first analgesia (TFA) or for block to completely wear off was noted. Visual analogue scale (VAS) pain scores were recorded at TFA and at 24 h, and analgesic consumption noted.

Four patients (one from each group) were withdrawn from the study owing to incomplete block (LBA and BA), unable to tolerate tourniquet (B) and a more minor operation being performed than planned (LB). Demographic variables were similar in all groups. Group BA had a significantly longer duration of block or TFA than both groups LB and LBA. VAS pain scores at TFA were similar; however, those at 24 h in the LB group were less than those in the two groups containing adrenaline. The 24-h morphine consumption was higher in both lignocaine groups (table 10).

*Table 10* Perioperative variables. Data displayed as mean (SD) or median interquartile range). Morphine consumption expressed as number (*n*) of doses. *$P<0.02$ for LBA and BA (ANOVA); †$P<0.05$ for LB and LBA; ††$P<0.05$ for LBA; **$P<0.02$ for LBA and BA (Kruskal-Wallis)

| | Group (*n*) | | | |
|---|---|---|---|---|
| | LB (13) | LBA (17) | B (12) | BA (16) |
| Block duration or TFA (h) | 10.7 (3.7) | 11.5 (3.3) | 12.3 (4.7) | 15.5 (4.8)* |
| 24 h | | | | |
| Morphine (*n*) | 0.7 (0.8) | 0.6 (0.6) | 0.2 (0.4)† | 0.3 (0.4)†† |
| Pain VAS | 8 (3–19)** | 29 (8–47) | 18 (9–34) | 31 (19–61) |

All groups provided good operative anaesthesia. The adrenaline-containing mixtures are a safe combination to use provided there is no pre-existing vascular insufficiency and vascular injection is avoided.

The BA combination provided the longest duration of postoperative analgesia and a low opioid consumption in the first 24 h. However, at 24 h this group had higher pain VAS scores. This may be related to either the low morphine consumption or perhaps the action of adrenaline which is involved in peripheral sensitization.

**Key words**
Anaesthetic techniques, ankle block.

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## Comparison of dural indenting between Whitacre and Quincke tipped spinal needles

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There is some concern over the increased failure rate for spinal anaesthesia with pencil point compared with conventional Quincke tipped spinal needles.[1] The reason for this may be because the lumen of the side hole is not entirely within the subarachnoid (SA) space at the moment when cerebrospinal fluid

(CSF) is first detected. This could result in partial failure to administer the local anaesthetic to the SA space. It has been suggested that this problem can be overcome by advancing the needle a further 1–2 mm from the point when CSF is first detected.[2] However, this would predispose the neural tissues to an increased risk of contact by the needle tip with resultant paraesthesia or damage.[3] We aimed to document and compare the amount of dural indentation which occurred before penetration of a blunt Whitacre (pencil point) and sharp Quincke tipped spinal needle during dural puncture.

We recruited 28 patients scheduled for elective TURP or TURBT under SA anaesthesia. Patients were randomized into two groups depending on whether a Whitacre 25 gauge or Quincke 25 gauge spinal needle was used. I.v. access and standard monitoring was established. Lumbar puncture was performed in the midline at the L2-3 interspace with the patient in the sitting position. After the needle was inserted into the ligamentum flavum, the stylet was removed and the needle connected to a pressure transducer. The needle was slowly advanced until the extradural space had been entered and the length of needle remaining outside the patient was measured (A). The needle was then advanced until a reduction in pressure was recorded; this is believed to be the point when the dura starts to indent. The length of needle is again measured (B). As the needle is slowly advanced, the pressure becomes progressively less until the dura is punctured, when a positive pressure indicates that the SA space has been entered. At this point the length of needle is once more measured (C). The distance between B and C represents the amount of dural indenting before puncture. With the study completed, patients were managed as usual.

Patient characteristics, extradural and subarachnoid distances and pressures were similar for the Whitacre and Quincke groups. In a similar proportion of subjects from each group only points A and C were identified. In the remaining subjects (*n*) in which indenting was seen, the pressure recorded just before dural puncture was significantly lower in the Whitacre group (table 11).

*Table 11* Data expressed as mean (SD) or median (IQ range) (*$P<0.02$ Mann-Whitney)

| | Group (n/N) | |
|---|---|---|
| | Whitacre (10/16) | Quincke (9/12) |
| Distance to dura (mm) | 1.5 (0.5–2.0) | 0.5 (0.5–1.0) |
| Dural indent (mm) | 2.25 (1.6–2.9) | 2.5 (1.5–3.0) |
| Lowest pressure (mm Hg) | −31.5 (−22.5 to −56) | −1.5 (0.5 to −5.5)* |

In a closed system, the dura was no more compliant when a Whitacre tip was used compared with a Quincke. However, a greater negative pressure was generated before the needle could puncture it. This would explain the palpable "click" experienced with these needles. The increased pressure gradient would favour retraction of the dura back to its original position. This evidence would favour the cessation of the practice of needle advancement which, in our view, is unnecessary.

**Key words**
Equipment, needles. Anaesthetic techniques, subarachnoid.

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## Enhanced spinal cord Fos expression following thermal injury in the mononeuropathic rat

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After nerve injury, altered processing of subsequent noxious stimuli may contribute to the development and maintenance of chronic pain states. The activation of pathways involved in spinal cord pain transduction can be mapped using the protein product of the immediate early gene *c-fos*; Fos protein being expressed rapidly in laminae 1-2 of the spinal cord as a monosynaptic response to C-fibre activation by peripheral noxious stimuli.[1] We therefore examined spinal cord Fos expression in response to thermal injury in a chronic constrictive nerve injury model of neuropathic pain.[2]

Male Sprague Dawley rats (five per group) were anaesthetized with halothane and underwent either loose ligation of the left sciatic nerve or sham operation: control animals underwent no surgery. Animals were allowed to recover for 14 days when animals in the stimulated group were re-anaesthetized and the left hind paw immersed in a water bath at 52 °C for 20 s; non-stimulated group animals were similarly anaesthetized but not exposed to the noxious thermal stimulus. Animals were allowed to recover for 2 h after which they were killed and Fos expression in the L4-5 spinal cord was quantified using an antibody to c-fos protein visualized by a diaminobenzidine peroxidase technique.[1] Data were expressed as means (SEM) and statistical analysis was by ANOVA with Bonferroni-Dunn correction.

Both nerve ligation and sham operation resulted in a persistent bilateral increase in Fos expression in laminae 3-4 and 5-10 when compared with control animals as has been reported previously.[3] However, little or no Fos expression in laminae 1-2 was evident in any non-stimulated animals. Thermal injury produced a large ipsilateral increase in laminae 1-2 Fos expression in all stimulated animals. Thermal injury caused significantly greater ipsilateral laminae 1-2 Fos expression in ligated animals than control animals ($P<0.01$); laminae 1-2 Fos expression in sham-operated animals did not differ significantly from control animals (fig. 16). Thermal injury did not significantly alter Fos expression in deeper laminae of the spinal cord in any animals.

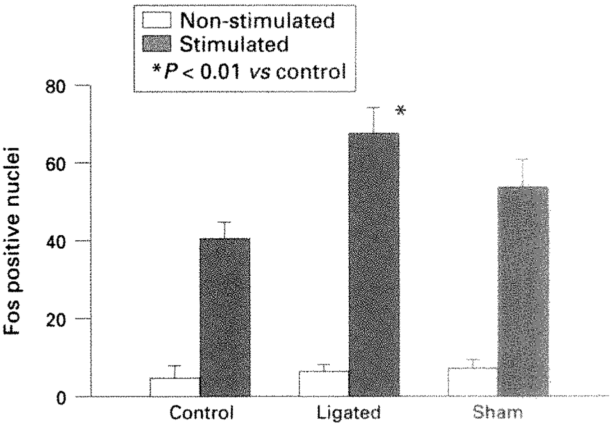

*Figure 16* Ipsilateral laminae 1-2 Fos (nuclei per section (SEM), n=5).

These data indicated that processing of nociceptive C-fibre afferent input was altered after neuropathic injury. Increased monosynaptic activation of dorsal horn neurones may be a result of enhanced C-fibre input and/or sensitization of central synaptic mechanisms.

**Key words**
Pain neuropathic. Rat. Genetic factors.

**Acknowledgement**

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# POSTER PRESENTATIONS

## Direct effects of suxamethonium on one paramyotonia congenita-mutant (R 1448H) of voltage-gated muscle sodium channels?

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Recently Vita and colleagues[1] reported two sisters suffering from myotonia fluctuans who presented masseter muscle rigidity and whole-body rigidity during induction of anaesthesia after suxamethonium. Myotonia fluctuans and other closely related disorders, for example, paramyotonia congenita (PC), are caused by several point mutations in the α-subunit of SCN 4A, the gene encoding the adult isoform of voltage-gated muscle sodium channels.[2] Therefore, we investigated possible direct effects of suxamethonium on one mutant sodium channel (R 1448H) causal in PC.

In human embryonic kidney cells expressing either the wild type (WT) or the mutant R 1448H of the human skeletal muscle sodium channel standard voltage-clamp whole-cell experiments were performed at 20 °C.[3] Control measurements were done in patched cells exposed to a stream of bath solution (140 mmol litre$^{-1}$ NaCl, 4 mmol litre$^{-1}$ KCl, 2 mmol litre$^{-1}$ Ca $Cl_2$, 1 mmol litre$^{-1}$ $MgCl_2$, pH 7.4, 284 mOsm). Thereafter, the same cells were exposed again to a stream of bath solution to which suxamethonium either 1 or 10 mmol was added. For steady-state activation (act) and inactivation (inact) the applied test pulses were plotted against normalized conductances. Boltzmann equations were fitted to the data yielding the voltage at half-maximum conductance ($V_{05}$) and the slope. Time constants for inactivation (τh) were obtained by bi-exponential fits to the decaying currents following voltage jumps from −100 mV to −30, −15, 0, 30 and 45 mV, respectively. Rate of recovery from inactivation at −100 mV was evaluated by a single exponential fit of normalized currents generated by test pulses to 0 mV which were plotted against the duration of the gap between 20 ms pre-pulses and test pulses to 0 mV. Statistic evaluation was performed by Wilcoxon and Mann-Whitney *U* test. $P<0.05$ was considered significant.

τh was significantly slower in R 1448H than in WT ($\bar{\tau}h_{R\ 1448H}=1.76$, range 1.2–2.35, $n=12$ *vs* $\bar{\tau}h_{WT}=0.45$, range 0.3–0.61, $n=11$ at 0 mV) with decreased voltage dependence of τh in R 1448H. In WT suxamethonium 1 mmol litre$^{-1}$ led to the following significant effects: shorter τh, left shift of $V_{05inact}$, left shift of $V_{05act}$ and enhanced maximum current. Besides a left shift of $V_{05inact}$ no significant effects of suxamethonium 10 mmol litre$^{-1}$ were found in WT. In R 1448H the same significant effects and, in addition, a delayed recovery were obtained only under suxamethonium 10 mmol litre$^{-1}$, whereas no significant effects of suxamethonium 1 mmol litre$^{-1}$ could be shown.

Our results confirmed recent reports[3] on marked electrophysiological differences between WT and R 1448H. These differences remained more or less unchanged by suxamethonium. The significant direct effects of suxamethonium found in this study were small, partly due to incomplete series resistance compensation and could not explain the above mentioned anaesthetic problems of patients suffering from hereditary sodium channel disorders. These were probably the result of depolarization itself.

**Key words**
Ions, ion channels. Ions, sodium. Biotrans formation, suxamethonium.

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## Effect of propofol on the uptake of propranolol into cultured cells

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The mechanism of action of anaesthetic agents remains largely unknown. However, there are a number of proposed mechanisms, and many of these involve nerve membranes and particularly ion channels or systems that regulate them.[1] It is thought that if the cell membrane or cell receptors were altered by anaesthetic agents, the uptake of other drugs into cells would be affected. This study was set up as a model for investigating this hypothesis, using propofol and the human neuroblastoma cell line SH-SY5Y. This established cell line expresses biochemical properties similar in characteristics to normal neuronal cells *in vivo*.[2] In this series of experiments, the model drug chosen was the lipophylic β adrenergic blocker, propranolol.

Cells of the human neuroblastoma cell line SH-SY5Y (passage 10-30) were cultured in Dulbecco's modified Eagle media (D-MEM) with 10% fetal calf serum, penicillin 100 IU ml$^{-1}$, streptomycin 50 μg ml$^{-1}$ and fungizone 25 μg ml$^{-1}$. Cells were fed twice weekly, and passaged with a 1:5 split ratio weekly. Cells became confluent after 7 days. Confluent cells were removed from T75 culture flasks and centrifuged to form a cell pellet. the cells were resuspended in 10 ml Hank's balanced salt solution (HBSS) without phenol red, and counted using the trypan blue exclusion method. The volume of media was adjusted to give $2\times10^6$ cells ml$^{-1}$.

One ml of cell suspension was aliquoted into 10 Eppendorf tubes. In the test group (five tubes), 10, 20 or 40 μl of 1 mmol litre$^{-1}$ propofol were added to each tube. In the control group (five tubes) 10, 20 or 40 μl of media were added to each tube. Cells were incubated in a waterbath at 37 °C for 10 min, after which 3H-propranolol 20 μl of 2 nmol litre$^{-1}$ (specific activity 25.0 Ci mmol$^{-1}$) was added to each tube. The tubes were incubated at 37 °C for 3 or 10 min, then centrifuged for 30 s in a microcentrifuge. The supernatant (incubation media) was removed and pellet was resuspended and washed in 1 ml of HBSS. The tubes were centrifuged for a further 30 s, and the supernatant (wash media) was removed. The cells were then resuspended in 1 ml HBSS. The incubation media, wash media and cell suspensions were transferred to scintillation vials, and 10 ml Optiphase 'Safe' added to each vial. Vials were inverted to ensure mixing of contents. All vials were then analysed on a Packard Tri-Carb Liquid Scintillation Counter, for 1 min. Each experiment (that is different volumes, different incubation times) was repeated 10 times.

The amount of 3H-propranolol in the cells was calculated as a percentage of 3H-propranolol in the media. The mean percentages of the 10 repeat experiments were calculated, and the means of the test and control data compared for all volumes of propofol and both 3H-propranolol incubation times. Results were compared using the Wilcoxon matched-pairs signed rank test.

Propofol appeared to inhibit the uptake of 3H-propranolol into cultured SH-SY5Y cells at all concentrations and incubations

*Table 12* Mean values and range for 3H-propranolol uptake (%) at the three concentrations of propofol after 3 and 10 min

| Volume of propofol (μl) | Control (range) | Test (range) | Difference | *P* value |
|---|---|---|---|---|
| 3 min | | | | |
| 10 | 40.2<br>(32.7–50.4) | 38.1<br>(26.3–49.1) | 2.1 | 0.0109 |
| 20 | 38.5<br>(30.1–49.2) | 35.3<br>(30.5–44.5) | 3.2 | 0.0125 |
| 40 | 37.6<br>(26.3–53.0) | 32.2<br>(22.1–43.0) | 5.4 | 0.0051 |
| 10 min | | | | |
| 10 | 39.8<br>(20.5–58.2) | 38.6<br>(20.1–57.2) | 1.2 | 0.0745 |
| 20 | 34.8<br>(26.0–42.9) | 30.7<br>(23.0–36.3) | 4.1 | 0.0051 |
| 40 | 37.5<br>(29.9–52.8) | 28.1<br>(17.3–41.8) | 9.4 | 0.0051 |

investigated (table 12). It also appeared that the inhibition is concentration-dependent.

The above method formed the basis of a model system to investigate the action of anaesthetic drugs on cells. From the results, it was not known how propofol inhibits the uptake of propranolol into the cultured cells. Further work using the same model will include using ion channel blockers and membrane perturbants to investigate if these agents have a similar effect on propofol uptake. Future experiments using this model might be useful for investigating the mechanisms of anaesthetic action.

**Key words**

Anaesthetics i.v., propofol. Model. Theories of anaesthetic action.

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### Only a small increase in end-expiratory pressure after cardiac surgery in Manchester

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Significantly raised end-expiratory alveolar pressures (EEP) have been shown to be common after cardiac surgery in Sweden.[1] This study, done in Manchester, was designed to investigate the duration of this raised EEP after surgery. In the event, few patients developed clinically significant EEP. This paper compared and contrasted the present observations with the Swedish ones.

There were 24 patients, all undergoing cardiac surgery; 20 were male. The mean age was 60 (range 38–73) yr. EEP was measured by pressing the "expiratory pulse hold" button on the Servo 900C ventilator. Readings were made (1) before sternotomy and (2) after sternal closure. The ventilator was set to rate 10 min$^{-1}$, inspiratory and pause times 25 and 10% of cycle.

Mean EEP in Manchester was 1.1 cm $H_2O$ (range 0–8) before sternotomy, increasing non-significantly to 1.9 (0–12) cm $H_2O$ after sternal closure. In Sweden mean EEP was similar before sternotomy, 1.9 (0–12) cm $H_2O$, but significantly ($P<0.005$) greater after sternal closure: 5.2 (0–21) cm $H_2O$. Mean age, and mean $FEV_1$ and VC as percentages of predicted, did not differ between the two countries; however some details of the anaesthetic and cardiopulmonary bypass (CPB) management did (table 13).

*Table 13* Comparison of intraoperative regimes in the two centres

| | Sweden | Manchester |
|---|---|---|
| Pre-CPB fluids | None | 0.5–1 litre |
| Ventilatory gases | $O_2/N_2O$ | $O_2$/air/enflurane |
| Ventilatory rate | 20 min$^{-1}$ | 10 min$^{-1}$ |
| Ventilation during CPB | Tidal volume 200 ml<br>Rate 10 min$^{-1}$ | No ventilation |

What can have caused the much greater EEP values seen in Sweden? Ventilating during CPB causes the same increase in lung water as not ventilating.[2] End-expiratory resistance was only slightly greater at small tidal volumes than large.[3] But in clinically important EEP, expiratory flow did not approach zero asymptotically. Indeed, the time constants late in expiration when EEP was raised were so large—several seconds—that doubling expiratory time could make no meaningful difference to EEP.

**Key words**

Ventilation, airway pressure. Ventilation, positive end-expiratory pressure.

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### Discriminating information in uncalibrated respiratory inductance plethysmography

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Stable calibration of respiratory inductance plethysmography (RIP) cannot be guaranteed over the long periods required for clinical observation. We examined the information content of unreliably calibrated RIP by seeing see how well effects on breathing pattern of two different infusion rates of alfentanil could be distinguished.

Two groups of eight consenting women were assigned randomly to receive double-blinded postoperative infusions of alfentanil 5 or 20 μg kg$^{-1}$ h$^{-1}$ after routine abdominal hysterectomy under standardized general anaesthesia. They were cared for and studied in a 24-h recovery room until the first postoperative morning by personnel who did not know what dose rate of alfentanil was being infused. Escape analgesia was provided as pethidine 50 mg every 2 h as necessary.

The ribcage and abdominal RIP signals were subjected only to an initial multiple regression calibration. A BBC microcomputer made on-line estimates of breath-by-breath tidal volume (VT), inspiratory time (TI) and expiratory time (TE), and stored them as the record of breathing pattern.[1] The records lasted for between 14 and 17 h, and consisted of between 6 and 32 periods of reasonably stable breathing interspersed with periods of disturbed pattern associated with non-respiratory movements such as talking, coughing, moving and being moved. Occasional brief disturbances were edited from periods of otherwise quiet breathing without reference to the dose rate of alfentanil, and the remaining breaths in each period were used to calculate the average VT, TI and TE, their coefficients of variation (cvVT, cvTI and cvTE) and the correlation coefficients between VT and TI for that period. A grand average of each of these seven within-period features of the breathing pattern was calculated for the whole study period for each of the 16 patients. Selections of grand average features of random selections of the patients were used to try to distinguish whether the remaining patients had been receiving a low or high dose of alfentanil. The power of discrimination was checked against the expectations of chance discrimination as described by binomial distributions. The analyses used the DISCRIMINANT procedure in MINITAB (run on an ELONEX PC-4100 microcomputer).

The overall average VT was the best single discriminator, and multiple discriminant models that included VT as an absolute measurement were more robust than models that did not. The best overall performance was from a model using VT, cvTI and cvTE. Models made from the grand average of the seven features of any 15 patients could use the seven features available from any single period of quiet breathing of the 16th patient and thereby identify the alfentanil dose received by that patient more often than expected by chance, significantly so ($P<0.05$) for all but three patients.

**Key words**

Measurement techniques, multivariate analysis. Measurement techniques, inductance plethysmography.

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### Effect of sevoflurane on spontaneous and evoked sympathetic activity in dogs

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A previous study has shown that desflurane at low concentrations causes a 30% increase in spontaneous sympathetic activity with

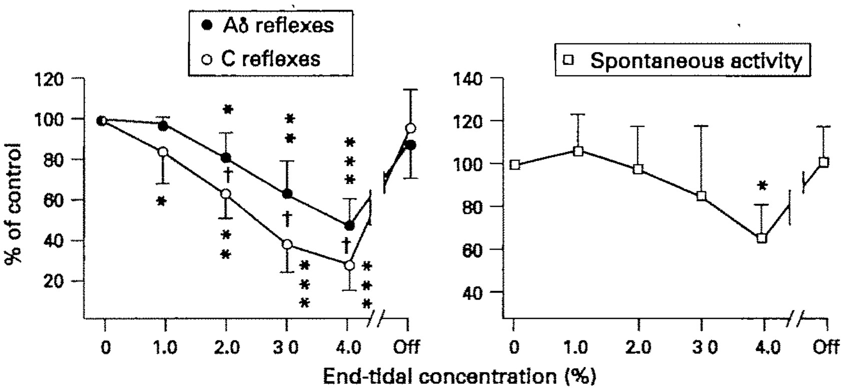

*Figure 17* Effect of sevoflurane on spontaneous and evoked sympathetic activity. Results are mean (SD) ($n$=5). Comparison with control: *$P<0.05$; **$P<0.01$; ***$P<0.001$. Comparison between Aδ and C reflexes: †$P<0.05$.

little depression of somatosympathetic reflexes. At higher concentrations, it depresses spontaneous and evoked sympathetic activity with a similar effect on Aδ and C responses. In contrast, isoflurane causes a dose-dependent depression in both spontaneous and evoked sympathetic responses with a relatively greater depression on C compared with Aδ reflexes.[1] This original observation has led to an ongoing study of the relative effects on sympathetic activity of the inhalational agents commonly in clinical use under similar conditions in the same animal model. The present study examined the effect of sevoflurane on spontaneous and evoked sympathetic activity in dogs and associated haemodynamic responses.

Experiments were carried out in five beagles anaesthetized (α-chloralose 15–20 mg kg$^{-1}$ h$^{-1}$), paralysed (suxamethonium 10 mg i.v. every 30 min) and artificially ventilated. Oesophageal temperature and blood gases were kept within the normal range. The radial and renal sympathetic nerves were exposed, desheathed, cut distally and mounted on silver electrodes in mineral oil pools. Supramaximal electrical stimuli (0.33 Hz, 50 V, 0.5 ms) were applied to the radial nerve. The evoked somatosympathetic reflexes were averaged, rectified and integrated. Spontaneous renal sympathetic discharges were amplified, rectified and integrated. Sevoflurane was administrated in each preparation to end-tidal concentrations of 1%, 2%, 3% and 4% for 20 min, respectively, after which measurements were recorded, and repeated 1 h after discontinuation of the agent.

Figure 17 shows the effect of sevoflurane on spontaneous and evoked sympathetic activity. It can be seen that at a 1% concentration there was no significant effect on Aδ reflexes but already C reflexes were depressed by 17% ($P<0.05$). By 4% the Aδ and C reflexes were 45.8% and 26.4% of control respectively ($P<0.01$). For spontaneous sympathetic activity there was no statistically significant decrease up to 3% but by 4% sevoflurane it was depressed to 64.1% of control ($P<0.05$).

Mean cardiac output remained unchanged up to 3% but decreased to 1.42 litre min$^{-1}$ from a control value of 1.64 litre min$^{-1}$ at 4% of sevoflurane ($P<0.05$). The mean MAP and systemic vascular resistance (SVR) markedly decreased in a dose-dependent manner from control values of 133 mm Hg and 6500 dyn s cm$^{-5}$ to 65 and 3654 at 4% sevoflurane respectively. The heart rate (HR) showed no significant decrease up to 3% but at 4% decreased to 132 beat min$^{-1}$ from the control value of 173 beat min$^{-1}$.

All variables returned to within control values after withdrawal of sevoflurane.

This study indicated that sevoflurane depressed Aδ- and C-fibre-mediated somatosympathetic reflexes in a dose-related manner, and that it had a greater effect on C compared with Aδ reflexes. At low concentrations it did not affect spontaneous sympathetic activity which was depressed significantly at higher concentrations. It decreased arterial pressure and SVR in a dose-dependent fashion and decreased cardiac output and HR at higher concentrations. There was no evidence of sympathetic excitation. The relative effect on C reflexes was greater than for isoflurane.[1]

**Key words**
Sympathetic nervous system. Anaesthetics volatile, sevoflurane. Dog.

**Acknowledgement**

This study was conducted under Home Office Licence (PPL 90/00852).

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## Association between inability to view the glottis at indirect laryngoscopy and difficult intubation: a preliminary assessment

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The association between the glottis view at indirect laryngoscopy and degree of difficulty of tracheal intubation has not previously been investigated. The principal aim of this preliminary study was to examine a group of confirmed difficult intubations and a control group of easy intubations to assess whether or not inability to view the glottis at indirect laryngoscopy was associated with difficult intubation.

Anaesthetists of all grades were asked to refer any patient that was assessed preoperatively as a potentially difficult intubation (whether they proved to be difficult or not) and any patient that was found to be difficult to intubate (whether this was suspected or not). The details of the laryngoscopy findings and the degree of difficulty of intubation were not known to the investigator until after the patient had been examined postoperatively. A control group of patients requiring intubation was also assessed. The patients were examined for Mallampati grade (as modified by Samsoon and Young[1]), interdental distance, thyromental distance, restricted neck mobility, mandibular protrusion and glottic visibility on indirect laryngoscopy.

Thirty-six patients were referred, of which there were 22 difficult intubations and 14 that were assessed preoperatively as potentially difficult that were found to be easy intubations. Nineteen of the difficult intubations were difficult direct laryngoscopies (that is, Cormack and Lehane grades III or IV[2]) with three patients being grade II laryngoscopies that required multiple attempts before the trachea was successfully intubated. A further 22 control patients were examined all of which were grade I laryngoscopies. The following patient features were selected as potentially predictive of difficult intubation: Mallampati grades III and IV, thyromental distance ≤7 cm, interdental distance ≤3.2 cm (mean of our results − 1 SD), moderate or severe limitation of neck movement, inability to protrude the lower incisors anterior to the upper incisors and inability to view beyond the epiglottis on indirect laryngoscopy. The association between each predictive test and difficult intubation was examined using chi-square and Fisher's exact test (where indicated).

There were 14 patients in the original group of 36 referred patients who had features to suggest difficult intubation but were found to be easy intubations. For the two tests with acceptable detection rates, that is Mallampati and indirect laryngoscopy, the number of wrong "difficult" predictions were 11 and 4 respectively (table 14).

*Table 14* Comparison of the performance of each predictive test on the difficult intubation group and the control group

| | Difficult intubations ($n$=22) | Controls ($n$=22) | |
|---|---|---|---|
| Predictive test | No. detected | False positives | $P$ |
| Mallampati | 16 (73%) | 6 (27%) | <0.01 |
| Thyromental distance | 4 (18%) | 0 (0%) | 0.1 |
| Interdental distance | 8 (36%) | 1 (5%) | 0.02 |
| Jaw protrusion | 3 (14%) | 0 (0%) | 0.2 |
| Neck mobility | 6 (27%) | 1 (5%) | 0.1 |
| Indirect laryngoscopy | 15 (68%) | 0 (0%) | <0.001 |

The association between failure to see the glottis at indirect laryngoscopy and difficult intubation needs to be tested prospectively before its use as a predictor of difficult intubation can be advocated.

**Key words**
Intubation tracheal, difficult. Anaesthesia, evaluation, preoperative.

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## Comparison of the immediate effects of induction of anaesthesia with etomidate, propofol and thiopentone on cerebral haemodynamics

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Most existing techniques of cerebral oxygenation monitoring are either invasive, require prolonged equilibration or involve ionizing radiation. Near infrared spectroscopy (NIRS) enables continuous non-invasive measurement of oxyhaemoglobin and deoxyhaemoglobin. Changes in cerebral metabolism and haemodynamics are known to occur after induction agent administration,[1] but their time course is difficult to study.

Thirty-six unpremedicated ASA grade I and II adult patients undergoing elective day-case surgery were studied. Oxyhaemoglobin and haemoglobin were recorded (Hamamatsu NIRO500) with an inter-optode spacing of 4 cm, with optodes located in the temporo-parietal region. The patients were allocated randomly to have anaesthesia induced with etomidate, propofol or thiopentone. Respiration was assisted as necessary to maintain normocapnia.

Areas under the concentration time curves of oxyhaemoglobin and haemoglobin were calculated to provide an index of changes in oxygenation of the brain against time. Groups were compared using a repeated measures ANOVA design, followed by $t$-tests with Bonferroni's correction.

After induction of anaesthesia, arterial saturation and end-tidal carbon dioxide did not significantly change. The area under the haemoglobin time curve did not significantly change either with respect to time ($P$=0.99) or induction agent ($P$=0.24) (table 15). The area under the oxyhaemoglobin time curve showed marked changes with respect to both time ($P$<0.001) and induction agent ($P$<0.001). Subgroup analysis showed that the decrease in oxyhaemoglobin seen in the etomidate group was significantly different from the increases seen with propofol ($P$<0.001) and thiopentone ($P$<0.001). The differences in oxyhaemoglobin between propofol and thiopentone were not significant.

*Table 15* Integrated oxyhaemoglobin and haemoglobin after induction of anaesthesia (mean (SD))

| | Etomidate | Propofol | Thiopentone |
|---|---|---|---|
| Haemoglobin ($\mu$mol litre$^{-1}$): | | | |
| 0–60 s | 0.44 (1.15) | −0.01 (0.72) | 0.26 (0.38) |
| 0–180 s | 0.81 (2.23) | 0.33 (4.68) | 0.82 (1.73) |
| Oxyhaemoglobin ($\mu$mol litre$^{-1}$): | | | |
| 0–60 s | −0.12 (2.05) | 0.32 (1.02) | 0.30 (1.09) |
| 0–180 s | −5.06 (6.89) | 9.27 (4.88) | 10.2 (10.0) |

This study showed that NIRS detected the small changes in oxygenation that occur during induction. These changes occurred within a time frame which only NIRS can detect at the bedside. The total amount of haemoglobin within the field of view is represented by the sum of haemoglobin and oxyhaemoglobin. Since haemoglobin remained unchanged, the changes in oxyhaemoglobin represented the change in total haemoglobin within the field. These changes occurred very shortly after loss of consciousness, at a time when no i.v. fluids were administered. Since the haematocrit would be expected to remain constant, it is likely that the change in the total haemoglobin signal was proportional to a change in the blood volume of the field of view. The increase in oxyhaemoglobin, at the same time as that in blood volume would suggest an increase in tissue oxygen saturation in the propofol and thiopentone groups. Similarly the decrease in oxyhaemoglobin in the etomidate group would suggest a decrease in tissue oxygen saturation.

**Key words**
Anaesthetics i.v., etomidate. Anaesthetics i.v., propofol. Anaesthetics i.v., thiopentone. Blood, haemoglobin. Blood, oxyhaemoglobin. Measurement techniques, near infra-red spectroscopy.

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## Blood gas changes during apnoeic oxygenation in infants and children

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Hypoxia develops rapidly during apnoea in young children breathing room air. A recent study in adults has demonstrated that stable gas exchange is achievable during continuous endobronchial insufflation of oxygen.[1] Given the lack of paediatric data, we determined to measure the changes in blood gas values of oxygen and carbon dioxide during apnoea after preoxygenation in small children.

After appropriate ethical consent, we studied 27 infants and children undergoing cardiac catheterization. Nineteen of the children were scheduled for PDA ligation and the others were known to have no major cardiac shunts. Anaesthesia was maintained with i.v. propofol infusion, fentanyl and pancuronium. At the end of the procedure, the patients were ventilated on 100% oxygen for 5 min down to an end-tidal carbon dioxide of 25 mm Hg. Ventilation was discontinued and the patient connected to a T-piece circuit with 1 litre min$^{-1}$ fresh gas flow. Blood gases were taken at 1-min intervals for 5 min and the study was abandoned if $P\text{CO}_2$ rose to 70 mm Hg, oxygen saturation decreased below 90% or the patient started to breathe.

Patients' ages ranged from 1 month to 13.3 years with a mean of 4.97 years. Five patients were less than 1 year old. Mean oxygen tension decreased from 557.4 (SD 83.7) mm Hg at the start of apnoea to 361.8 (94.5) mm Hg by 5 min. Most of the decrease in oxygen tension occurred during the first minute (103.9 (50.0) mm Hg). Carbon dioxide tension increased from 27.6 (3.1) mm Hg at the start of apnoea to 54.5 (10.7) mm Hg at the end of 5 min (fig 18). Surprisingly, the values for changes in blood gases during apnoea from this study are similar to the adult data: oxygen decrease after the 1st min averaged 11.3 mm Hg min$^{-1}$ [range 17–48.9] while the increase of carbon dioxide averaged 3.5 mm Hg min$^{-1}$ [range 1.6–7.5]. Only one patient needed

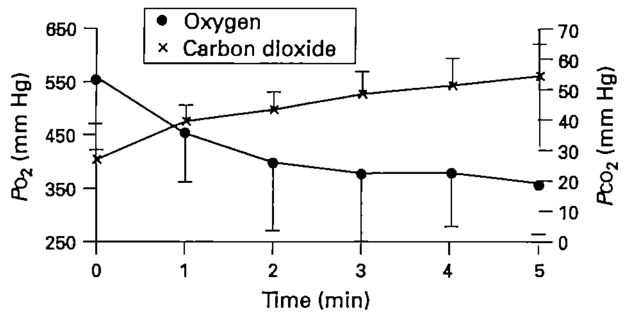

*Figure 18* Changes in blood gas values in children during apnoea after preoxygenation for 5 min. All values are means (SD).

to be withdrawn from the study because of decreasing oxygen saturation. There did not appear to be a relationship between age and changes in oxygen and carbon dioxide during apnoea.

**Key words**

Anaesthesia, paediatric. Lung. Ventilation.

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## Interaction of lignocaine with recombinant opioid receptors expressed in Chinese hamster ovary cells

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Local anaesthetics have been reported to enhance opioid analgesia.[1] However, it is still unknown whether local anaesthetics interact with opioid receptors. In this study, we examined the interaction of local anaesthetics with recombinant, μ, κ or δ opioid receptors expressed in Chinese hamster ovary (CHO) cells, (CHO-μ, κ or δ, respectively).

All studies were performed with membranes prepared in TRIS-HCl 50 mmol litre$^{-1}$, pH 7.4 by homogenization and centrifugation. Binding assays were performed in 1-ml volumes of TRIS-HCl 50 mmol litre$^{-1}$, pH 7.4, for 90 min at room temperature using approximately 200 μg of protein. Non-specific binding was defined in the presence of naloxone $10^{-5}$ mol litre$^{-1}$. Bound and free radioactivity were separated by vacuum filtration. In displacement studies, the interaction of lignocaine $10^{-6}$–$10^{-2}$ mol litre$^{-1}$ with μ, κ and δ-opioid receptors was determined by displacement of [$^3$H]diprenorphine 0.5 nmol litre$^{-1}$. Saturation analysis to determine the equilibrium dissociation constant (*K*d) and the maximal binding capacity (Bmax) of CHO-μ, κ or δ in the presence and absence of lignocaine were performed using increasing concentrations of [$^3$H]diprenorphine 0.03–3.0 nmol litre$^{-1}$. *B*max and *K*d were obtained from Scatchard plots. The concentration of lignocaine producing 50% displacement of specific binding ($IC_{50}$) were obtained by computer assisted curve fitting (GRAPHPAD-PRISM) and corrected for the competing mass of [$^3$H]diprenorphine according to Cheng and Prusoff[2] to yield the affinity constant (*K*i). All data were expressed as mean (SEM) ($n \geq 5$).

*Table 16* *K*d (pmol litre$^{-1}$) and *B*max (fmol mg$^{-1}$ protein) values for [$^3$H]diprenorphine binding to CHO-μ, κ or δ membranes in the absence and presence of lignocaine (*μ: $P$=0.0004, κ: $P$=0.0228, δ: $P$=0.0001 Student's *t*-test)

| | Bmax | *K*d |
|---|---|---|
| δ | 279 (4) | 372 (15) |
| +2.5 mmol litre$^{-1}$ lignocaine | 287 (3) | 674 (13)* |
| μ | 272 (3) | 85 (5) |
| +1.0 mmol litre$^{-1}$ lignocaine | 263 (6) | 209 (9)* |
| κ | 70 (2) | 91 (6) |
| +0.3 mmol litre$^{-1}$ lignocaine | 66 (3) | 167 (16)* |

[$^3$H]diprenorphine binding was dose dependent and saturable with *K*d (pmol litre$^{-1}$) and *B*max (fmol mg$^{-1}$ protein) values shown in table 16. Lignocaine dose-dependently displaced diprenorphine binding to all opioid receptors with the following rank order potency (p*K*i) κ (3.68 (0.02))>μ(3.26 (0.04))>δ (2.74 (0.03)) Lignocaine increased the *K*d of diprenorphine without affecting the *B*max, consistent with an allosteric interaction at opioid receptors. Further studies on the nature of the interaction and whether this could contribute to the reported analgesic effects[1] are currently under way in out laboratory.

**Key words**

Analgesics opioid, receptors. Anaesthetics local, lignocaine. Model, hamster.

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## Oxygenator exhaust capnography as an index of arterial carbon dioxide tension during cardiopulmonary bypass employing a membrane oxygenator

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A previous report described the use of oxygenator exhaust capnography ($PE_{CO_2}$) as a monitoring technique during cardiopulmonary bypass employing a bubble oxygenator.[1] During the cooling and stable hypothermic phases of cardiopulmonary bypass the relationship with arterial carbon dioxide tension ($Pa_{CO_2}$) was reasonably accurate, but became far more variable during rewarming. We have investigated the relationship between $PE_{CO_2}$ and $Pa_{CO_2}$ during hypothermic cardiopulmonary bypass with non-pulsatile flow employing a membrane oxygenator.

Thirty-two patients undergoing cardiopulmonary bypass had oxygenator exhaust gases channelled into 100 cm of elephant tubing from the midpoint of which gases were sampled by a side-stream capnograph. Five min after institution of cardiopulmonary bypass and at 15-min intervals thereafter the capnograph reading was recorded and an arterial blood sample drawn for measurement of $Pa_{CO_2}$ by a bench blood gas analyser. An additional sample was drawn and measurement recorded at 34 °C during rewarming.

A total of 172 paired measurements were made. The degree of agreement between paired measurements ($Pa_{CO_2}$ and $PE_{CO_2}$) at each time point was calculated using the method of Bland and Altman[2] (fig 19).

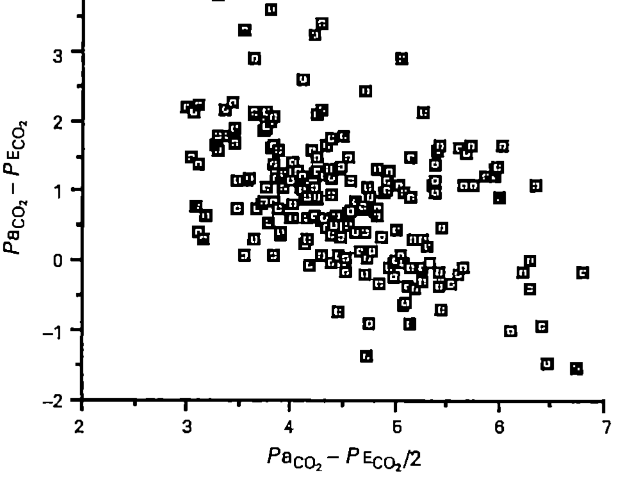

*Figure 19* Relationship between the difference between measurements (y axis) and the mean of the measurements (x axis) at each time point (all measurements).

Mean difference was 0.9 kPa (d) with a standard deviation of 0.99 kPa (s) (95% limits of agreement −1.09 to 2.88 kPa (L)). Results were further analysed during stable hypothermia (n=30, d=1.88, s=0 69, L=0 5 to 3.26), rewarming at 34°C (n=32, d=0, s=0.84, L=−1.28 to 1.28), rewarming at normothermia (n=48, d=0.15, s=0.69, L=−1.23 to 1.53) and with (n=78, d=0.62, s=0.99, L=−1.36 to 2.6) or without (n=91, d=1.07, s=0.9, L=−0.91 to 2.88) carbon dioxide running. No relationship was detected between either $Pa_{CO_2}$ or $PE_{CO_2}$ and core body temperature, pump blood flow or oxygenator gas flow.

We found no useful relationship between carbon dioxide concentration in exhaust gases from a membrane oxygenator during cardiopulmonary bypass and $Pa_{CO_2}$.

**Key words**
Surgery, cardiovascular. Monitoring techniques, capnography.

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*British Journal of Anaesthesia* 1997; **78:** 476–482

# CORRESPONDENCE

## Intraoperative gut hypoperfusion may be a risk factor for postoperative nausea and vomiting

Sir,—We read with interest the article on nausea and vomiting after cardiac surgery by Grebenik and Allman.[1] There are two issues which we believe are important but were not discussed by the authors.

Gut mucosal hypoperfusion is common after cardiac surgery and may be another factor that explains the high associated incidence of postoperative nausea and vomiting.[2] Animal studies have shown that damage to the gut is accompanied by an increase in 5-HT$_3$ in gut mucosa.[3] Radioligand binding studies demonstrated the presence of large number of 5-HT$_3$ receptors on vagal terminals that innervate the intestinal mucosa and on the same vagal afferent nerves located in the brain stem vomiting centre.[3] Furthermore, it has been demonstrated recently that plasma volume expansion during cardiac surgery is associated with maintenance of gut perfusion and reduction in postoperative morbidity, including persistent nausea and vomiting.[4]

The authors mentioned that "if the patients did not meet the criteria for tracheal extubation and required sedation to tolerate intubation and ventilation, an infusion of propofol 1–4 mg kg$^{-1}$ h$^{-1}$ was commenced until another trial of spontaneous breathing was performed at the discretion of the nursing staff" Propofol is an antiemetic in its own right. Numerous studies have shown that propofol as a primary agent for maintenance of anaesthesia was associated with a lower incidence of postoperative nausea and vomiting.[5,6] When used in this manner, it is more efficacious than ondansetron 4 mg.[7] We have defined plasma concentrations of propofol for effective treatment of PONV as 405 ng ml$^{-1}$ (95% confidence interval 280–530 ng ml$^{-1}$).[8] Data from computer simulation using the pharmacokinetic variables of Gepts and colleagues[9] demonstrated that infusion of propofol 1–4 mg kg$^{-1}$ h$^{-1}$ for sedation, as used by the authors, produces plasma propofol concentrations in the effective range for treatment of nausea and vomiting for up to 180 min after termination of infusion (fig. 1). However, they did not provide information on the number of patients treated with propofol and the duration and dose of propofol used in each group, which may affect the overall results.

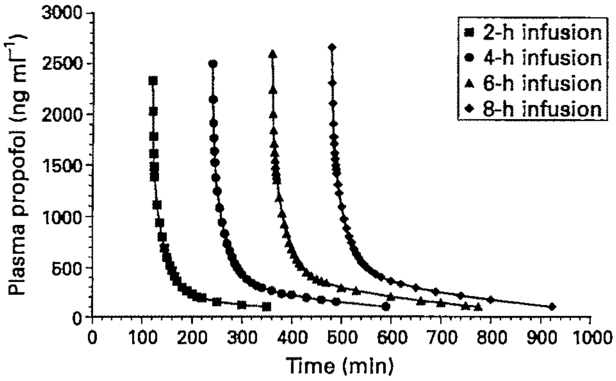

*Figure 1* Simulated plasma decay of propofol concentrations after 2-, 4-, 6- and 8-h infusions.

Hence it is important to specify the details of propofol administration in studies that investigate the incidence of PONV.

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Sir,—Thank you for the opportunity to respond to the comments of Gan, Mythen and Glass. While gut mucosal hypoperfusion may be among the factors that are associated with postoperative nausea and vomiting (PONV), I would guess that this is not confined to cardiac operations and may well contribute to PONV after other types of major surgery.

Propofol undoubtedly possesses antiemetic properties. All our patients received an infusion of propofol during cardiopulmonary bypass. Patients whose tracheas were extubated immediately after return to the recovery unit would still have had propofol concentrations in the effective range for treatment of PONV at the time of tracheal extubation. Similarly, those patients who required a period of propofol sedation after operation would also have had therapeutic concentrations at tracheal extubation. We did not measure the amounts of propofol given, but duration of intubation did not differ significantly between our two groups. Given the large number of patients in each group ($n=200$ and $n=198$) it seems likely that the amounts of propofol given were similar in each group. Thus while propofol used either during anaesthesia or in the early postoperative period may have exerted an antiemetic effect during the first 2 h after tracheal extubation, this does not alter our findings that addition of droperidol to a continuous infusion of morphine was effective in reducing nausea and vomiting after cardiac surgery.

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## Ethanol monitoring during hysteroscopy

Sir,—The complications of endometrial resection were reviewed by Williamson and Mushambi in an editorial in the September issue of *British Journal of Anaesthesia*.[1] The importance of fluid absorption in this context is emphasized by the fact that several fatal cases of the "female TUR syndrome" have occurred.[2,3] In their article, the authors did not recommend the ethanol method for monitoring fluid absorption because they could not account for the sex-related differences in breath ethanol and serum sodium responses to fluid absorption that were described by me in a recent review article.[4]

I have stated that the ethanol response to fluid absorption is 10% greater in middle-aged women undergoing endometrial resection than in elderly men undergoing transurethral resection of the prostate. This difference is easy to account for as most women are of a smaller size than men. The authors' distrust, however, was probably elicited by my suggestion that the serum sodium response to fluid absorption is 40% greater in females than in males. The magnitude of this difference can be illustrated by assuming that 1000 ml of irrigating fluid containing 1.5% glycine with 1% ethanol is absorbed by a male and a female. My nomograms suggest the reduction in serum sodium concentrations would amount to 8 mmol litre$^{-1}$ in males and 11 mmol litre$^{-1}$ in females.[4] Is this difference reasonable? Yes, I think so. The amount of extracellular water in the extracellular space, which is the distribution volume for sodium, has been reported to be 200 ml/kg body weight in males and 150 ml/kg body weight in women.[5] Based on these data, the difference that I have reported is what would be expected.

I admit that in the original study of fluid absorption by myself and Olsson, 62 patients were too few in number to allow construction of a nomogram.[6] However, as stated in my review article, the published nomogram was also based on a series of additional patients (up to a total of 70) who actually absorbed irrigating fluid. One of the additional cases has been described to show the elegance with which the ethanol method works.[7]

The "fluid deficit" is suggested in this editorial to be the best indicator of fluid absorption during hysteroscopy. This implies routine use of volumetric fluid balance. However, many factors need to be controlled to make routine use of this method accurate.[4] To my knowledge, its sensitivity has never been tested. Poor correlations between key variables which should all reflect fluid absorption are usually reported in studies where the method seems to have been used on a routine basis. My group has had difficulty obtaining useful data with it during prostatectomy.[8] The fluid deficit needs to be compared with more precise methods of measuring fluid absorption before I would recommend it as a standard method. As far as ethanol monitoring is concerned, several such studies have been conducted and its accuracy and precision are well known.

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Sir,—We thank Professor Hahn for his interest in our editorial on complications of hysteroscopic treatments of menorrhagia,[1] and we are grateful for his comments.

It was not the aim of our editorial to exclude the ethanol method for estimating fluid absorption during transcervical endometrial resection (TCER). As stated by Professor Hahn both in his letter and in his review,[2] the nomograms for estimating fluid absorption from expired ethanol concentration during TCER were based on few patients. Incidentally, his review article stated that the TCER nomograms were based "on 62 patients with the addition of a few more patients with large scale absorption". Therefore, while the method has been investigated and used extensively during transurethral resection of the prostrate (TURP) we feel that more research and experience is necessary before we can recommend it for routine use during TCER. There is no doubt that, despite its limitations, volumetric fluid balance is still the most commonly used method of assessing fluid absorption during TCER. We agree with Professor Hahn that ethanol monitoring is a non-invasive, easy and accurate method of assessing fluid absorption during TURP. Hopefully in the near future this will also be applicable to its use during TCER.

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## ACE inhibitors and renal protection

Sir,—I read with interest the article by Licker and co-workers[1] and agree that angiotensin converting enzyme (ACE) inhibitors may be of some value in renal protection during surgery. In a previous study we found that aortic cross-clamping-induced haemodynamic changes were less marked in enalapril-treated patients compared with controls,[2] in agreement with the study of Licker and colleagues. However, regarding renal perfusion, we established that effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were not maintained at baseline levels during aortic cross-clamping in enalapril-treated patients, although ERPF and GFR were good before clamping.[2] Licker and colleagues established that ACE inhibitors were effective in improving renal perfusion during aortic abdominal surgery and this seems to refute our own conclusions. In fact, these differences may be explained easily.

Their renal haemodynamic studies showed that aortic cross-clamping induced a significant decrease in ERPF in controls only (approximately −21%). However, although this decrease in ERPF in enalapril-treated patients was not statistically significant (approximately −14%), the renal blood flow:cardiac output ratio decreased significantly only in enalapril-treated patients (−25%); this strongly suggests that blood flow was redistributed away from the kidney during clamping. Moreover, although not statistically significant (but the number of enalapril-treated patients was small), the mean increase in renal vascular resistance and mean decrease in GFR during aortic cross-clamping (+43% and −20%, respectively) were not less relevant than the decrease in ERPF in controls. The data may have been confusing therefore because the threshold of statistical significance was not reached because of the small number of patients studied. Moreover, patients had different pathologies, notably both aortic aneurysm and atherosclerotic occlusive disease.

In my opinion, Licker and colleagues cannot assert that, in contrast with calcium antagonists,[2] ACE inhibitors prevent the renal vasoconstrictive effect of infrarenal aortic abdominal cross-clamping. Nevertheless, I agree that ACE inhibitors may boost renal perfusion before and after aortic clamping.

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Sir,—We thank Dr Colson for his comments. We acknowledge that the small sample size of the study precludes firm conclusions concerning the haemodynamic changes induced by renin–angiotensin system block. The numbers of patients whose renal data were evaluated were nine and 11 for the saline and enalapril groups, respectively. At $P<0.05$ this number of patients was sufficient to detect a significant decrease in ERPF from a mean value of 472 to 371 ml $min^{-1}$ after aortic cross-clamping in the saline group whereas the (ns) changes observed in the enalapril group (from 582 to 499 ml $min^{-1}$) may represent a type II error. If we assume similar ERPF values in larger groups ($n=69$), "true differences" would have been reached for (within and between) group comparisons while maintaining a power of 0.90 ($\beta=0.10$); such data would confirm lesser impairment of renal haemodynamic state after pretreatment with enalapril.

During aortic cross-clamping, the renal blood flow:cardiac output ratio (RBF:CO) decreased by 25% in enalapril-treated patients and this was attributed entirely to a decrease in RBF as there was no change in CO. In contrast, proportional changes in RBF and CO were observed in saline-treated patients resulting in an unchanged RBF:CO ratio. Activation of unblocked vasopressor support systems (such as arginine vasopressin and the sympathetic nervous system) in response to aortic clamping could be implicated in the renal vasoconstriction in the two groups. In addition, the systemic haemodynamic pattern suggested that enalapril-induced vasodilatation was effective in renal and extrarenal vascular tissues; these data agree with experimental data supporting the notion that the splanchnic vascular bed is more sensitive to the vasoconstrictor effects of sympathetic stimulation and angiotensin II.[1 2]

The beneficial renal haemodynamic effects of enalapril were demonstrated clearly in the present study as: (1) the RBF:CO ratio increased before aortic cross-clamping as a result of a greater increase in RBF compared with CO, (2) during aortic clamping, ERPF was reduced to a lesser extent, (3) a greater glomerular filtration rate (GFR) was maintained; GFR and ERPF were strongly associated ($r=0.65$ in the enalapril group) after aortic clamping, implying that approximately 40% of the observed changes in GFR could be explained by haemodynamic variability.

Taken together, our preliminary data suggest lesser impairment of renal perfusion and function during aortic abdominal surgery after enalapril pretreatment.

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## Possible mechanism to explain increased coagulability of blood after haemodilution

Sir,—We read with interest the discussion ensuing from the article by Ruttman, James and Viljoen[1] on hypercoagulability of blood after administration of i.v. crystalloids. Farmery and Kong[2] suggested that the results "challenge intuitive assumptions". We suggest that an increase in coagulability is reasonable for the following reasons. Blood coagulation is controlled by continuous interaction between pro- and anticoagulant factors. Haemodilution reduces the concentration of anticoagulant factors as much as procoagulant factors. Thus there is no intuitive reason to assume that anticoagulation would occur any more than procoagulation. A procoagulant effect could easily be brought about if the concentration–effect relationship of the anticoagulant factors were initially steeper than that of the procoagulant factors, that is dilution reduces the effect of anticoagulant factors more rapidly than procoagulant factors. This makes sense teleologically, where coagulability should increase after haemorrhage when blood volume is re-expanded with interstitial fluid.

As pointed out by the above authors, regional anaesthesia reduces the incidence of deep vein thrombosis despite the likely need for increased crystalloid administration. A possible explanation is that regional anaesthesia reduces the surgical stress response and its associated procoagulant effects. Could it be that crystalloid "primes" the coagulation system by the above proposed mechanism, and that the procoagulant tendency is then activated by surgical stress? We feel that these considerations would explain the observations reported, although we accept that evidence to confirm or refute them is not yet available.

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Sir,—We thank Fletcher and Heard for their comment on our article. The argument they make that anticoagulant factors are diluted to the same degree as procoagulant factors is valid, and has been suggested previously by Monkhouse,[1] who suggested that haemodilution may disturb the ratio of thrombin to antithrombin III. An imbalance between the two may predispose to a procoagulant effect. Subsequent *in vivo* data, which are currently under consideration for publication, suggest that antithrombin III is decreased to a greater extent after haemodilution than could be explained by haemodilution alone, the inference being that the act of haemodilution *per se*, had induced the conversion of prothrombin to thrombin with subsequent thrombin–antithrombin III interaction. The suggestion by Fletcher and Heard that this effect may have a teleological basis is particularly elegant, as it could explain the reason for its occurrence.

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## Regional anaesthesia in moyamoya disease

Sir,—We have read the article of Ngan Kee and Gomersall on extradural anaesthesia for Caesarean section in a patient with moyamoya disease.[1] We wish to describe our own experience with an elective Caesarean section managed with spinal anaesthesia in a patient with moyamoya disease.

A 34-yr-old woman suffered intraventricular bleeding in her 24th week of pregnancy, requiring intensive care and mechanical ventilation for 8 days. During this period the only unusual problem was development of pneumonia. She recovered without any sequelae and moyamoya disease was diagnosed by arteriography. The patient remained healthy for the remainder of the pregnancy and in the 38th week an elective Caesarean section was planned. Preoperative investigations were normal, including anticardiolipin antibody concentrations. After a preload of 1000 ml of lactated Ringer's solution, a left radial artery cannula and central venous catheter (via the antecubital fossa) were inserted under local anaesthesia. Analysis of arterial blood was carried out at 15-min intervals. Anaesthesia was performed with 0.5% spinal bupivacaine 15 mg and fentanyl 50 μg at L2–3, using a 25-gauge Whitacre needle, and 28% oxygen was given by face mask. The level of sensory analgesia to pinprick was T5. Total intraoperative fluid given was 1500 ml of mild lactated Ringer's solution. There were no changes in heart rate, direct arterial pressure or temperature, apart from transient hypotension (80% of preoperative value) treated with ephedrine 15 mg i.v. A healthy 3250-g male baby was delivered with Apgar scores of 8 (1 min) and 9 (5 min).

After surgery the patient remained in the PACU for 6 h and was discharged uneventfully without any change in her neurological status. There were no other problems in the subsequent 3 months.

Several cases have been reported of patients with moyamoya disease managed successfully with general anaesthesia for Caesarean section.[2] In our opinion, regional anaesthesia is preferable for these patients in order to obviate intubation-induced hypertension and the risk of aspiration. Some cases have also been reported using extradural anaesthesia.[3] However, the complication rate is less with spinal anaesthesia.[4] We believe that avoidance of hypotension, or treating it carefully, allows the use of spinal anaesthesia in these cases. By avoiding hypotension, hypothermia and hyperventilation, there were no neurological signs in our awake patient whose conscious state and cerebral function could be observed continually. A case of convulsions after spinal anaesthesia in a child with moyamoya disease has been reported,[5] probably caused by changes in cerebral blood flow (CBF). We believe that these convulsions occur more frequently in younger patients with moyamoya disease and may be avoided by strict management of CBF. The doses of bupivacaine used for extradural anaesthesia are higher than those used in spinal anaesthesia, with increased risk of neurological and cardiological problems.

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Sir,—Thank you for the opportunity to reply to Drs Llorente de la Fuente, Gimenez Garcia and Lopez Sanchez. Although they have described the successful use of spinal anaesthesia for Caesarean section in a patient with moyamoya disease, we believe this is not the optimum technique in this circumstance. While we concur that regional anaesthesia has advantages over general anaesthesia, we believe that extradural anaesthesia is preferable to spinal anaesthesia.[1] Llorente de la Fuente, Gimenez Garcia and Lopez Sanchez have emphasized the importance of strict management of cerebral blood flow in these patients. We sought to achieve this by inducing central neural block gradually under close monitoring; we believe the slower onset of sympathetic block in extradural anaesthesia is more amenable to accurate titration of interventions compared with spinal anaesthesia.[2]

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# Converting pH and H$^+$: a "rule of thumb"

Sir,—Many centres have changed to the use of hydrogen ion concentration (H$^+$) rather than the traditional pH when dealing with acid–base problems. Converting H$^+$ to pH or vice versa is very simple when tables are available. We propose a straightforward method for conversion when they are not.

We have observed that, between pH values of 7.10 and 7.60, the sum of the hydrogen ion concentration (in nmol litre$^{-1}$) and the numerical value of the two digits after the pH decimal point is relatively fixed around 83, the mean of these sums in this pH range (table 1).

*Table 1* Method for conversion of H$^+$ to pH

| pH | 7.00 | 7.10 | 7.20 | 7.30 | 7.40 | 7.50 | 7.60 | 7.70 |
|---|---|---|---|---|---|---|---|---|
| H$^+$ | 100 | 79.4 | 63.1 | 50.1 | 40 | 31.6 | 25.1 | 20 |
| Sum | 100 | 89.4 | 83.1 | 80.1 | 80 | 81.6 | 85.1 | 90 |

To convert pH from H$^+$, the numerical value of the two digits after the pH decimal point is calculated by subtracting H$^+$ from 83. For example, if H$^+$ is 70.8 nmol litre$^{-1}$, the estimated value of pH would be (7.83−70.8), or 7.12. The actual pH value at this hydrogen ion concentration is 7.15.

To convert H$^+$ from pH, the numerical value of the two digits after the pH decimal point is subtracted from 83. Therefore, if pH is 7.50, the estimated value of H$^+$ would be 83−50, or 33 nmol litre$^{-1}$. The actual hydrogen ion concentration at this pH is 31.6 nmol litre$^{-1}$.

The errors are small and clinically inconsequential for conversions performed between pH values of 7.10 and 7.60. We feel that our simple "rule of thumb" will be useful to doctors dealing regularly with clinical situations in which acid–base disturbances are a feature.

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# Local anaesthesia to the airway reduces sedation requirements in patients undergoing artificial ventilation

Sir,—We read the article of Mallick, Smith and Bodenham[1] with interest and wish to make a few comments. In their study, although the use of local anaesthetic solution reduced the need for sedation in patients who underwent ventilation, it also suppressed the cough reflex. Patients appeared to be less bothered by pulmonary suctioning. The technique may be safe if used for short periods but our concern is that, if used over a longer period it may increase the risk of pulmonary infection.

Mucociliary clearance is an important mechanism of pulmonary defence. Effective mucociliary clearance depends on the function of the cilia and their coordinated beating.[2] Corssen and Allen[3] studied ciliary function in tracheobronchial epithelium obtained with a punch biopsy and found that lignocaine caused a dose-related but reversible effect on ciliary activity. At low doses ciliary beating was stimulated and as the dose increased the cilia stopped beating. In contrast, amethocaine and cinchocaine caused irreversible stoppage of ciliary activity. It is clear that topical anaesthesia may cause areas of ciliary dysfunction and could predispose to airway colonization and pneumonia. The effects of long-term local anaesthesia on ciliary motility have not been studied.

We believe that further studies are needed to evaluate the effect of local anaesthetics on respiratory epithelium. One suggestion is to compare the effect of local anaesthetics on mucociliary clearance using either a dye or a radio-opaque contrast as a marker. If the use of topical anaesthesia is found to be safe, then reduced requirements for sedatives may prove beneficial and may reduce the morbidity and mortality of patients undergoing artificial ventilation.

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## Anticholinesterases and subsequent duration of block of suxamethonium

Sir,—I read with interest the article by Fleming and colleagues[1] on the effects of anticholinesterases on subsequent duration of block with suxamethonium. The clinical observations are clear and in accord with conventional wisdom.

The authors have however fallen into a common trap with regard to their interpretation of the cholinesterase activity values. Their pooled data are in accord with those of Viby-Mogensen,[2] who they referenced, in that over the clinical range the correlation between measured activity and duration of suxamethonium block is poor. In this study, a correlation can be shown clearly only in the presence of extremely low levels of measured activity. Another part of the problem is that the substrate used is not that used clinically (suxamethonium) but a thiocholine derivative, and that the correlation between different assay techniques and suxamethonium sensitivity is less than ideal.[3]

In addition, although not stated by the authors, such measurements of cholinesterase activity involve a large dilution of the plasma sample; this varies between laboratories but is usually 30–300-fold dilution into the reaction mixture. For cholinesterase inhibitors with prolonged covalent binding such as neostigmine, any inhibition produced would be likely to persist over a short period of dilution. Neostigmine concentrations decrease rapidly *in vivo* to approximately $6 \times 10^{-7}$ mol litre$^{-1}$.[4] This concentration is associated with approximately 50% inhibition of cholinesterase activity (unpublished personal data, see fig. 1) and accords with the authors observations. Other less tightly bound agents such as edrophonium[5] would be expected to be associated after such dilution with a lower inhibition than might be predicted from plasma concentrations at the time of sampling. The assumption that enzyme inhibition measured after dilution *ex vivo* accurately reflects *in vivo* conditions is a common but erroneous one.

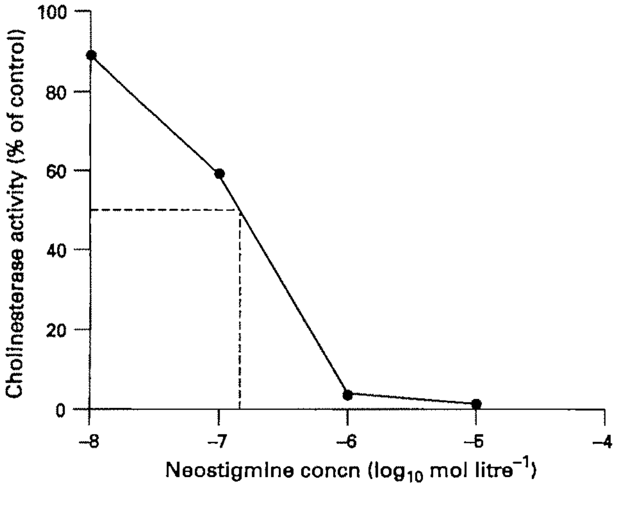

*Figure 1* Effects of neostigmine on plasma cholinesterase catalysis. Data are means of repeated measures of plasma from a normal individual. The assay is a modification of that of Ellman and colleagues.[6]

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Sir,—We thank Dr Graham for his interest in our work and appreciate the opportunity to respond to his comments. Although we beg to differ as to whether the interpretation of our results constitutes "falling into a common trap", we feel his letter highlights some limits of our studies and emphasizes aspects of this work which could benefit from further discussion.

We agree that although Viby-Mogensen described the most commonly referenced relationship between measured activity of plasma cholinesterase and the duration of action of suxamethonium,[1] when cholinesterase activity is in the normal clinical range, the slope of this graph is indeed shallow. The hyperbolic relationship he plots is largely determined by values outside the normal range. Although the sensitivity of the plasma cholinesterase activity assay for detection of less active variants of the enzyme may be improved slightly by the use of alternative substrates as described by Evans and Wroe,[2] their study focuses on the detection of less active variants of the plasma cholinesterase enzyme, not on the characteristics of normal enzyme which has been exposed to a cholinesterase inhibitor. It is the effects of the mechanism of inhibition which we believe deserve emphasis.

As non-competitive inhibitors which react to form a carbomoylated cholinesterase enzyme, neostigmine and pyridostigmine are unlikely to be affected by assay techniques which include a dilutional step. In contrast, edrophonium, as a competitive inhibitor, may be profoundly affected. This may explain the contrast between studies which demonstrate minimal inhibition of plasma cholinesterase activity by edrophonium[3 4] while the metabolism of other substrates (e.g. mivacurium) is inhibited.[4]

For non-competitive inhibitors, dilutional effects on enzyme activity measurements should be at best, minimal, and at worst, comparable. There is no evidence that the substrate used for the assay should have a differential sensitivity for these chemically related inhibitors. In our studies, pyridostigmine produced profound inhibition of plasma cholinesterase (79% of baseline) compared with neostigmine (48% of baseline). In contrast, the duration of action of suxamethonium increased only 35% after pyridostigmine compared with 78% after neostigmine. Despite the limitations of the enzyme activity assay, we believe this contrast provides the strongest evidence that this is a much more complex drug interaction than previously realized.

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## I.v. anaesthetics and binding to calcium channels

Sir,—The article by Hirota and Lambert[1] demonstrating an interaction between a variety of i.v. agents and the dihydropyridine binding site on L-type voltage-sensitive $Ca^{2+}$ channels is an interesting addition to the bewildering literature on mechanisms of anaesthesia.

The concept that i.v. anaesthetic agents may reduce neurotransmitter release via diminished influx of calcium ions is attractive as calcium influx is the common trigger for neurotransmitter release in invertebrates and vertebrates.

The authors hypothesize that i.v. anaesthetics may act via inhibition of calcium influx through L-type channels. Although their discussion may appear convincing, there are reservations with this hypothesis.

First, L-type channels do not seem to be crucial to stimulus–secretion coupling in the majority of vertebrate preparation studied[2–5] as this coupling is generally insensitive to dihydropyridine antagonists. If the likely target for anaesthetics is transmission across central synapses, then the significance of L-type calcium channel inhibition for anaesthesia may be minimal. Interestingly, other calcium channels, for example P and N channels, have been implicated in neurotransmitter release in vertebrate neurones.[3,4]

Second, are the authors, therefore, observing non-specific actions of anaesthetic agents rather than actions which underlie anaesthesia? Stereospecific differences in anaesthetic effects are seen at the receptor level for isoflurane on the $GABA_A$ receptor.[6] Hypnosis may also be stereospecific.[7]

Although it is perhaps too early to say if stereospecificity may be a marker for actions that are relevant to the mechanism of anaesthesia, it is worthy of note that the anaesthetic effects of isoflurane on L-type calcium channels do not demonstrate stereoselectivity.[8,9]

Third, the overwhelming fact remains that traditional dihydropyridine antagonists have minimal action as anaesthetics in the conventional sense, even if the blood–brain barrier is crossed.

I believe that these considerations significantly weaken the case for inhibition of calcium influx in L-type channels being an important mechanism of action of i.v. anaesthetic agents.

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Sir,—We thank Dr Wilkinson for his interest and comments on our article.[1]

Before we respond to his detailed comments we wish to state clearly our position. We are not totally convinced that voltage-sensitive $Ca^{2+}$ channels (VSCC) have a role to play in anaesthesia but we are equally not convinced that they do not. We feel that it is premature to exclude this important class of ion channels as anaesthetic target sites and hoped that this is what our article and a recent editorial[2] conveyed. We agree that the literature is bewildering but as Dr Wilkinson points out, inhibition of VSCC and hence neurotransmission is an attractive site for anaesthetic action.

While our article was concerned specifically with L channels (probed using the radiolabelled dihydropyridine $[^3H]$PN200-110) we do not exclude other types of VSCC, such as P and N channels, as target sites for anaesthetic agents and this was also noted in our recent editorial.[2] Indeed, studies with radiolabelled conotoxin (specific for N channels) are currently at the planning stage. Dr Wilkinson cites several studies that show neurotransmitter release is not controlled by L channels and in general we agree with this. However, there are reports showing that L channels are involved (see Spedding and Lepagnol[3]). Of particular interest to us is the SH-SY5Y human neuroblastoma cell line that we have used in several studies of the mechanism of action of i.v. and volatile general anaesthetic agents. In this cell line L channel-mediated noradrenaline release and $K^+$-evoked increase in $[Ca^{2+}]_i$ are inhibited by thiopentone, propofol, ketamine, etomidate and halothane.[4–7] Moreover, we feel that modulation, by classic L channel agonists and antagonists, of ethanol, barbiturate and benzodiazepine potency[8,9] indicates something important! In addition, L-VSCC blockers have antinociceptive actions which are known to contribute to anaesthesia.[10–13]

There is strong support for the $GABA_A$ receptor as a target site for anaesthetic agents[14] and we have never disputed this fact. Stereoselectivity is noted for the $GABA_A$ receptor for a range of resolved anaesthetic agents. However, as Dr Wilkinson points out "it is perhaps too early to say whether stereospecificity may be a marker for actions that are relevant to the mechanism of anaesthesia".

The point made regarding the "non-anaesthetic" effect of L channel antagonists is well taken but it still remains that in experimental animals L channel agonists and antagonists modify ethanol, barbiturate and benzodiazepine potency.[8,9] In addition, Nacif-Coelho and colleagues reported that direct administration of L channel ligands into the locus coerulus modified the anaesthetic potency of dexmedetomidine in the rat.[15] Collectively, these data suggest that provided passage of the blood–brain barrier is facilitated, L channel blockers can have "anaesthetic-like" effects.

In summary, our studies with L channels form a basis for further studies with N and P channels and we feel that it is premature to exclude the voltage-sensitive $Ca^{2+}$ channel as a target site for anaesthetic agents.

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*British Journal of Anaesthesia* 1997; **78:** 483–485

# BOOK REVIEWS

*Pain Relief and Anesthesia in Obstetrics.* A. VAN ZUNDERT AND G. W. OSTHEIMER. Published by Churchill Livingstone, New York. Pp. 1062; indexed; illustrated. Price £100.00.

This book comprises 101 chapters set out in seven sections, with contributions from 179 authors, mainly from the USA, but some from Europe, Scandinavia, South America, Australia, New Zealand, Canada and Lebanon. Most chapters give the views of authors from more than one continent, often giving American and European perspectives.

Following an introduction by two well known obstetric anaesthetists (G. Marx and P. R. Bromage) and a brief history of pain relief in childbirth, the first section covers physiological and pharmacological influences in the mother, fetus and neonate. Chapters in this section are well written and illustrated. However, the chapter on maternal assessment gave a European view which may not be a true representation of clinical practice in the UK and possibly Europe. I find it hard to believe that most European obstetric anaesthetists warn patients about the occurrence of Homer's syndrome as a complication of extradural analgesia. This chapter also states that a woman in labour may be denied extradural analgesia if she has not attended a prepartum consultation, unless the obstetrician makes a personal request on clinical grounds.

The second section covers extradural analgesia for obstetric pain relief. It includes anatomy of the spine and pharmacology of drugs used. The chapter on the anatomy of the lumbosacral spine is well written and illustrated. The chapter on the pharmacology and toxicity of local anaesthetics is, on the whole, well written but the authors have failed to mention the maximum doses of local anaesthetics. The North American emphasis of the book is highlighted in this section, particularly by the choice and use of drugs and drug names.

Section three covers alternative analgesia during labour and delivery. This includes topics such as TENS, acupuncture, hypnosis, systemic opioids, inhalation analgesia and other regional blocks. The use of spinal analgesia during labour is covered in great detail, including the use of combined spinal–extradural (CSE) analgesia. The clinical features and management of post-dural puncture headache (PDPH) are well covered and there appears to be no conflict in the approach to PDPH between the USA and Europe.

Section four sets out to describe the anaesthetic management of Caesarean delivery, and again, most chapters in this section offer European and American views. Anaesthesia for Caesarean section includes extradural, spinal, general and local anaesthesia. Many of these chapters are good, despite a significant amount of repetition of both extradural and spinal anaesthesia from a previous section. Included in this section is a chapter on post-Caesarean section analgesia. Unfortunately, this chapter would not be comprehensive enough for British anaesthetists. It does not mention the use of extradural diamorphine for postoperative pain relief or the use of adjuvant analgesics, such as non-steroidal anti-inflammatory drugs, which are commonly used in the UK.

Section five is a comprehensive account of the high-risk parturient and her fetus. This section covers a wide range of topics such as pregnancy-induced hypertension (PIH), cardiac and other systemic diseases, embolism, difficult intubation and aspiration of gastric contents, morbid obesity and drug addiction in the pregnant woman. Most chapters include views from continents other than North America. The chapter on cardiac diseases was readable and well done, however, I wonder if the authors did really mean to say that an ejection fraction of 0.82% is normal.

Section six deals with maternal and neonatal outcome. The chapter on maternal mortality includes the *Confidential Enquiry into Maternal Deaths in the UK* but unfortunately the latest report to be mentioned is from 1990. Hence some of the recommendations from the 1994 report are not included. Other interesting topics which have been included in this section are anaesthesia for fetal surgery, anaesthesia for *in vitro* fertilization procedures and management of the parturient after transplant surgery.

The seventh and final section covers administrative problems and controversies in obstetric anaesthetic practice. The editors have aimed to include obstetric anaesthetic services from various countries, including some developing countries. Unfortunately, the quality of these chapters was variable. Some chapters were disappointing. Finally, the chapter on standards for obstetric anaesthetic services covered only American standards and failed to mention those of any other country, such as the minimum standards recommended by the Obstetric Anaesthetists Association in the UK.

Overall, the editors of this book have been successful in covering a wide range of topics. As may be expected from the large number of contributors, there is significant repetition. It is surprising however, that on occasions, the same author repeated him/herself. The inclusion of views of several authors on one topic sometimes implied that each account gave insufficient detail for the reader to achieve full understanding. This was most obvious with the chapter on pregnancy-induced hypertension. A more comprehensive chapter by one author might have given enough detail and would have been more readable. The American emphasis was dominant throughout the book which makes it more useful for the American obstetric anaesthetist. The lists of references are good but the relative paucity of reference to publications after 1990 is disappointing for a book published in 1996. Although this is a book that I would not buy for personal use, it is well worth consideration for reference in a departmental library.

*M. C. Mushambi*

*Baillière's Clinical Anaesthesiology—Neuroprotection, vol 10, No. 3.* J. A. STAMFORD AND L. STRUNIN (editors). Published by Baillière Tindall, WB Saunders, London. Pp. 214; indexed; illustrated. Price £30.00.

The aim of this book is to update anaesthetists on the present position regarding research and development of drugs and other therapeutic means of limiting the detrimental effects of cerebral ischaemia. The editors state that the reader will benefit from reading the book as a whole rather than only selected chapters, and this is undoubtedly the case. I would recommend anyone who is interested in neuroprotection to read the whole volume The individual chapters deal with laboratory models of cerebral ischaemia, cerebral energy metabolism, neurotransmitters in cerebral ischaemia, role of calcium in ischaemic brain injury, modulation of voltage-gated sodium channels, antagonists of excitatory amino acids, free radicals, anticonvulsants and reperfusion injury, general anaesthetics as neuroprotective agents, acute management of head injury, physiological imaging of stroke and the future of neuroprotection. They provide an up-to-date description of the pathophysiological processes thought to be involved in cerebral ischaemia and a thorough evaluation of the efficacy and likely future role of pharmacological and other proposed methods for limiting neuronal damage.

The chapters are well written with useful explanatory illustrations and are pitched at the correct level for clinicians. Each chapter ends with a useful short summary of the important points and there are comprehensive lists of references at the end of each chapter. The system of referencing sometimes makes the text difficult to follow and the publishers might consider changing to the system of numbered references used by the major anaesthetic journals.

I enjoyed reading this book and learnt much from it. It achieves its aim of updating practising clinicians on the subject of neuroprotection. All anaesthetists could benefit from reading it but it will be particularly useful for intensivists, neuroanaesthetists, cardiothoracic and vascular anaesthetists. It would also make useful reading for neurosurgeons and physicians involved in the management of stroke. Therefore, it will be an important addition to the shelves of all postgraduate medical libraries.

*E. Moss*

*A Short History of Anaesthesia: The First 150 Years.* G B. RUSHMAN, N. J. H. DAVIES AND R. S. ATKINSON. Published by Butterworth Heinemann, Oxford Pp. 218 Price £16.99.

This is a lovely little book, produced primarily by the Southend team and thus owing much to the late Dr J. Alfred Lee to whose memory it is dedicated. Much of the book is based on his earlier writings in the various editions of *Synopsis of Anaesthesia*, but with the material updated and making particular reference to the many major anniversaries between 1994 and 1998.

Squeezed within its slim covers are 20 chapters and three appendices covering almost every conceivable aspect of the specialty. The first four chapters outline developments sequentially and the remaining 16 review the history of specific topics, culminating with a calendar of major events. The appendices review the organization of the specialty, early publications on anaesthesia and a bibliography of the history of anaesthesia. Each section is obviously short, but the entries are anything but superficial and the references are the really key ones. The text is as authoritative as it is comprehensive and I could find no fault with the descriptions of those aspects of the history of anaesthesia that are of particular interest to me. The volume is reminiscent of T. E. Keys' *The History of Surgical Anesthesia*, but is more up to date and more structured. This allows the reader to find material sought much more readily.

It is my firm view that anyone who is interested in anaesthesia should own a copy of this book. It would make a superb introductory text for the beginner in anaesthesia because it provides an introduction to all aspects of the specialty in a very digestible form. For everyone else it provides a definitive reference source for settling arguments and acting as a stepping stone in a search for more detailed information in the literature. I repeat, this is a lovely little book.

*J. A. W. Wildsmith*

*Pain Clinic Manual.* S. DOLIN, N. PADFIELD AND J. PATEMAN (editors). Published by Butterworth Heinemann, Oxford. Pp. 310; indexed; illustrated. Price £30.00.

The *Pain Clinic Manual* is a new book aimed at consultants, trainees, junior doctors and nurses with an interest in the management of patients with chronic pain. There are 16 contributors of whom 25% are consultant anaesthetists who specialize in pain management. Contributors from other specialties include a rheumatologist, palliative care consultant, dentist, clinical psychologist and an orthopaedic surgeon. This reflects the increasingly multidisciplinary approach to pain management and is to be commended.

The book is divided broadly into seven parts. The first part contains chapters on the pain clinic, pain patient and measurement of pain. These provide a reasonable introduction to the topic, but would benefit the trainee by containing more modern references. Part two has chapters on generalized pain patterns. The chapter on reflex sympathetic dystrophy clearly identifies the problems with diagnosis and treatment of this difficult condition, and contains 110 references (possibly a little excessive for a manual!). The third part is the largest and has chapters describing pain by anatomical location. For the most part the contributors have adhered to a similar structure for each chapter (anatomy, classification, clinical features, examination, investigation and management) which makes for easy reading. Two chapters are devoted to back pain, appropriately reflecting the large proportion of patients being referred for this difficult problem. I was concerned that one of the recommended treatments of disc prolapse was strict bedrest. It is suggested further that analgesics have little benefit, and there was no mention of physiotherapy. There are few enough clinical guidelines in pain management but they do exist for the treatment of back pain; surely we should be using them.

Part four of the book pertains to common pain problems and is generally well organized with the same structure as the previous part. Microvascular decompression (MVD) is recommended in the treatment of trigeminal neuralgia if percutaneous techniques have failed, however percutaneous procedures may reduce the success rate of MVD. Outcome studies are obviously required. In fact the general lack of outcome studies in pain management is an extremely important observation echoed by many of the contributors. The fifth part includes helpful chapters on symptom control in cancer and in human immunodeficiency disease. Information on psychological therapies and pain management programmes are addressed in the sixth part of the book and are succinct and relevant. Lastly there is a chapter on the future which suggests that the prevention of or early intervention in the treatment of chronic pain should be the way forward. The appendices on invasive procedures contain helpful technical and clinical advice.

The quality of the chapters, illustrations and references is variable, which is to be expected from a book with this number of contributors. However, my overall impression is that, despite some inconsistencies, the manual provides a reasonable guide to the problems encountered in the pain clinic and the therapeutic options available. At £30.00 the *Pain Clinic Manual* is a worthwhile investment and I would recommend it for those who need an easy guide to the management of patients as they present to the clinic.

*F. A. Campbell*

*Cardiac Surgery: Safeguards and Pitfalls in Operative Technique*, 2nd Edn. S. KHONSARI. Published by Lippincott Raven, New York. Pp. 339; indexed; illustrated. Price £149.50.

This publication is the second edition of a work first published in 1988. It is a textbook devoted to operative technique in cardiac surgery, highlighting safeguards and pitfalls. It is predominantly a single author's experience, namely Dr Siavosh Khonsari, of the University of California, Los Angeles. He acknowledges the collaboration and contribution of his colleague, Dr Colleen Sintek. The aim of the text is to provide a practical guide to surgeons in training and it also offers tips and hints that surgeons of all levels of experience will find interesting. The text is presented in a manner that is simple and easy to read.

The first three sections of the book cover general considerations of the cardiac surgical patient and surgery for acquired heart disease, including ischaemic heart disease. The techniques described are largely up to date, which is a difficult feat to achieve in a rapidly changing specialty. The topic of minimally invasive coronary artery surgery is mentioned but not described in major detail and this is understandable. No mention is made of minimally invasive techniques for valve surgery. The latter half of the book is devoted to surgery for congenital heart disease. The illustrations are excellent and potential errors in operative technique are described clearly. Interestingly, the technique of intraoperative echocardiography as a method of determining the effectiveness or otherwise of surgical treatment is not mentioned. This would have been particularly appropriate in the chapters relating to intra-cardiac repair of congenital abnormalities.

With this one criticism, I consider that this textbook is a well written guide and deserves a place in the library of any department of cardiac surgery. It is probably too expensive for surgical trainees to purchase for personal use.

*M. St J Hickey*

*Ambulatory Anaesthesia and Surgery.* P. F. White (editor). Published by WB Saunders, London. Pp. 918; indexed; illustrated. Price £90.00.

The chief editor's stated goal in writing this book was to create a comprehensive reference source which emphasized the "team concept" of health care delivery in this field. To achieve this no fewer than 119 contributors (29 of whom are non-anaesthetists) and eight consulting editors have produced a book of more than 900 pages, containing up-to-date material, referenced data and expert opinion of a very high standard

The text is divided into eight sections: five of these deal with clinical aspects commencing with "preoperative assessment and preparation" and "surgical considerations and concerns". "Pharmacologic principles and applications" deals with basic pharmacokinetics and individual drug groups and includes a chapter on techniques of local anaesthesia. "Assessing recovery and outcome" deals comprehensively with everything from PONV to re-admission rates, and the final clinical section deals specifically with the management of children.

Two non-clinical sections deal with organization, management, medical economics and legal issues, covering with great thoroughness the essential requirements for, and development of, an ambulatory surgery centre. The discussion on financial matters has much of relevance to the anaesthetist working in a purchaser/provider environment, despite the American scenario.

The eighth section is an interesting "international perspective" with contributors from 17 different areas of the world describing ambulatory surgery in their country. The final pages of the book contain seven problem-orientated case studies which highlight some of the clinical dilemmas which may present to health care workers in this field

The text is long, detailed and very thoroughly referenced, using 88 pages of named references, each of which usefully details all the chapters of the book in which that reference is used. There is liberal use of photographs, figures, tables and diagrams, and overall the presentation is excellent. Almost every aspect of ambulatory anaesthesia and surgery is covered in a clear and easily understood manner. The use of American English and syntax and a setting within the American health care system presents less of a problem nowadays; the language of the modern NHS and the competitive, financial climate of trusts make a book such as this understandable and it contains much information which is relevant to hospital medicine and anaesthesia in general, out-with the day-care unit

There are minor eccentricities: quoting Sir Lancelot Spratt and using more than three pages to describe the contents of a crash cart; and irritations such as MAC means "monitored anaesthesia care", but these do nothing to diminish the value of this book. It is well prepared and edited and surprisingly readable, used as either a reference work or for casual reading. I recommend it for all departmental libraries where it will be of great interest to all those who are involved with day-case surgery and anaesthesia.

*D Raitt*

*British Journal of Anaesthesia* 1997; **78**: 486

# ERRATUM

*British Journal of Anaesthesia* 1997; **78**: 39–43.

There were four sets of mistakes in this article:

*p. 39:* In the summary, "$HbO_2$+Hb (Hbdiff)" should read "$HbO_2$−Hb (Hbdiff)".

*p. 40:* In the last sentence in the left-hand column, "The measured variables, oxygen saturation, end-tidal carbon dioxide, cerebral oxygenated and deoxygenated haemoglobin concentration, CBV, arterial pressure and heart rate were averaged over 2-s epochs, down-loaded onto a lap-top computer and analysed using software developed for monitoring intracranial pressure and waveform analysis" should read "The measured variables, oxygen saturation, end-tidal carbon dioxide, cerebral oxygenated and deoxygenated haemoglobin concentration, ***v*mca**, ......".

*p. 42:* Similarly, in the right-hand column, second paragraph, last sentance, ***v*mca** should replace CBF in the sentence begining "In our experiments, CBF appeared ......".

*Figures 2–5:* The legends to these figures should read "Cerebral blood **volume** (CBV)" and not "Cerebral blood flow", as printed.

We apologize to the authors for this confusion.

*"I would have everie man write what he knowes and no more."*—MONTAIGNE

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## EDITORIAL

### Effect of blood transfusion on postoperative immunocompetence

The 20th century has seen the establishment of blood transfusion as an essential part of modern medical practice, and many advances in the treatment of patients, especially in the field of surgery, would have been difficult, if not impossible, without the availability of human blood products. Along with the acceptance of blood transfusion as a beneficial form of therapy has come the realization that the collection, storage and transfer of blood from one human to another is not without risk. Side effects of transfusion range from mild allergic reactions, through bacterial and viral infection, to more serious immune-related reactions such as acute haemolysis (table 1). Febrile, non-haemolytic reactions complicate 1% of transfusions; the risks of acquiring viral hepatitis or the human immunodeficiency virus (HIV) are estimated at 1 in 5000 and 1 in 400 000, respectively (in the USA), and the risk of a fatal haemolytic reaction is approximately 1 in 600 000.[1–3] One side effect of blood transfusion that has received relatively little publicity in recent years, partly overshadowed by public and professional concern over the risk of HIV transmission, and partly because of continuing controversy over its clinical significance, is immunosuppression.

*Table 1* Detrimental side effects of blood transfusion

| | |
|---|---|
| Immunological: | Febrile reactions<br>Urticaria<br>Alloimmunization<br>Hypersensitivity reactions<br>Haemolytic reactions (immediate/delayed) |
| Infective: | Viral<br>Bacterial<br>Protozoal |
| Volume related: | Cardiogenic (e.g. pulmonary oedema)<br>Metabolic (e.g. hyperkalaemia, hypocalcaemia)<br>Clotting disorders |

## History

Medawar was one of the first to study the immunomodulatory effect of blood transfusion in 1945 when, in a series of animal experiments, he demonstrated a commonality of antigens between blood and other tissues.[4,5] As a consequence of his findings the early transplant surgeons adopted a policy of deliberately avoiding blood transfusions, as far as was possible, in potential transplant recipients, believing that if a patient was exposed to foreign antigens from a transfusion there was a very real chance that similar antigens may later be presented to a transplant, leading to rejection. Over the next 30 yr clinicians realized instead that blood transfusion actually appeared to protect renal allografts, and in 1973 Opelz and colleagues published a large retrospective study of patients who had undergone renal transplantation, demonstrating that graft survival was increased by up to 20% in those who had received a transfusion before transplantation.[6] The greatest benefit was seen in patients receiving five or more transfusions, and it appeared that transfusion of blood was responsible for down-regulation of the recipient's immune system in some way. Over the next 10 yr the attitude of transplant surgeons changed from one of deliberate avoidance to that of deliberate transfusion. Units developed procedures for both donor-specific and random donor transfusion, resulting in an increase in the 1-yr graft survival rate from 40% to 60%.[7]

## Mechanisms of immunomodulation

Despite the progress in our understanding of immunology there is, as yet, no clear explanation as to how transfusion of allogenic blood causes suppression of the recipient's immune function. Some authors believe that transfusion itself is not responsible for a so-called "transfusion effect", rather that it is a surrogate marker for some other event that is responsible; in the case of transplant surgery that transfusion pre-selects patients who will not become sensitized to donor antigens, and in the case of other disease processes that transfusion is a marker for severity of disease or treatment, or both, which would automatically place the subject in a worse prognostic group.[8,9] It is well recognized however that blood transfusion suppresses some aspects of the immune system, giving rise to depressed delayed hypersensitivity reactions, decreased natural killer cell activity, decreased CD4/CD8 ratios and decreased IL2 production.[10–14] There are several theories to explain these effects: *clonal deletion*—the presence of foreign MHC antigens causes deletion or inactivation of T cells with receptors for that MHC, and may occur centrally (thymic deletion) or peripherally (non-thymic deletion); *tolerance*—essentially failure to respond to antigenic stimulation, possibly by blocking of receptor sites on T cells; *active suppression*—cellular immunity may be actively down-regulated either by suppressor T cells or by sub-groups of helper T cells specific for humoral immunity.[8,15–18] It is not yet clear which of the many components of a blood transfusion is responsible for causing immunomodulation but donor leucocytes carrying foreign antigens appear the most likely, and work with leucodepleting filters for transfusions has shown amelioration of the transfusion effect.[11 12 19 20]

## Current interest

Although initial realization of the immunomodulatory effect of blood transfusion arose in the field of transplantation, the advent of powerful immunosuppressive agents (cyclosporine A in particular) and improvements in patient care (both before and after operation), patient selection, HLA matching, rejection therapy and graft perfusion/ transportation techniques, have reduced the "transfusion effect" in transplantation to negligible levels.[21] In recent years clinicians have considered if the immunosuppressive effects of transfusion may influence other aspects of patient care, and for those treating patients at or around the time of surgery (a time when the need for transfusion often arises) the concern has been whether transfusion may affect the original disease process, and whether it may contribute to patient morbidity during the recovery period. As far as postoperative immunocompetence is concerned, the three main areas of interest have been: (i) tumour recurrence rates, (ii) postoperative infection rates and (iii) clinical course of inflammatory disorders such as Crohn's disease.

## Tumour recurrence

The first report of a transfusion effect other than in transplantation was in the early 1980s when Burrows and Tartter reported their results of a retrospective review of colorectal cancer patients, demonstrating a positive association between perioperative blood transfusion and cancer recurrence.[22] Using multivariate analysis to control for covariate factors they concluded that blood transfusion was the second most important prognostic variable, after pathological staging. This first report of such a link between blood transfusion and cancer prognosis stimulated interest around the world, and to date nearly 100 studies on this subject have been published, some of which support and others which dispute the presence of such an association.[23] The majority of these studies examined colorectal cancer which is both common and often requires blood transfusion as part of its management, thus yielding large numbers for study.[24–28] The remainder have examined cancer of the breast,[29 30] lung,[31 32] kidney,[33 34] prostate,[35 36] stomach,[37 38] cervix,[39] vulva,[40] head and neck,[41 42] bone[43] and soft tissue sarcoma.[44]

The majority of this work has been retrospective in nature, and the conclusions reached by the different authors clearly demonstrate the dichotomy of international opinion. Even meta-analyses of the combined results of these studies reflect this disagreement, some showing a positive association between transfusion and tumour recurrence,[45 46] while others maintain such an association is caused by confounding variables not controlled for by the retrospective nature of the studies.[23 47]

## Postoperative infection rates

Renal allograft survival and cancer recurrence rates are both long-term markers of clinical outcome, whereas postoperative infection usually manifests within 7–14 days of surgery and would be expected to be more prevalent in patients who are immunosuppressed to a significant degree. The same workers in America who first reported on cancer recurrence rates published their results of postoperative infection rates among transfused and non-transfused patients a few years later.[48] They found an increase in infection rate from 4% to 25% which was independently associated with perioperative blood transfusion. Increased infection rates of similar magnitude have been reported for abdominal surgery,[11 49] orthopaedic surgery,[50 51] cardiac surgery[52] and trauma patients.[53 54] Overall these studies appear more supportive of the idea that perioperative blood transfusion has a deleterious effect on patient outcome, even when combined and subjected to meta-analysis.[45 55] This acceptance is still not universal, and there remains a body of opinion that this association is caused by other variables for which controls are not adequate.[56]

## Inflammatory disorders

Far less well reported is the effect that perioperative transfusion has on the clinical course of Crohn's disease, a condition which may be autoimmune in nature. Two studies have shown a 2–3-fold increase in disease recurrence in patients who were not transfused at the time of surgery, compared with those who were.[57 58] The numbers of patients in both studies were small but if the effect was real it may represent a beneficial aspect of transfusion-related immunomodulation similar to that described for transplant patients.

## Discussion

Transfusion-related immunosuppression is a real phenomenon, the mechanism of which is currently unknown. The questions facing clinicians who are responsible for transfusing patients are: is the transfusion effect clinically significant, and if so what can we do to avoid it? The debate over significance will continue until sufficiently large, controlled clinical studies provide an answer on which authorities can agree.[18 56] Transfusion of homologous blood can be avoided to a certain extent by several means in both elective and emergency surgery (table 2)[59 60] and there are several filtration systems available which can remove up to 99.9% of leucocytes from red cell products either in the blood bank or at the bedside. Until such time that more hard evidence is available

*Table 2* Methods of avoiding homologous blood transfusion

| |
|---|
| Greater use of crystalloid/colloid volume expanders |
| Meticulous haemostasis |
| Pre-deposit autologous transfusion |
| Preoperative recombinant erythropoetin |
| Iso-volumic haemodilution |
| Intraoperative blood salvage |

the issues outlined above should be used as one consideration in the decision of whether or not to transfuse. There is no doubt that judiciously timed transfusions in the perioperative period for patients who are losing significant quantities of blood are essential, but the morbidity and mortality risks of transfusion must be considered carefully in all cases.[61–64]

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CLINICAL INVESTIGATIONS

# Extradural pain relief in labour: bupivacaine sparing by extradural fentanyl is dose dependent

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**Summary**

The minimum local analgesic concentration (MLAC) of bupivacaine in labour is defined as the effective concentration in 50% of subjects ($EC_{50}$). We have used the technique of double-blinded sequential allocation to quantify the bupivacaine sparing effect of the addition of four different doses of extradural fentanyl in 223 labouring women. There were five groups: (1) plain bupivacaine (control); (2) bupivacaine with fentanyl 1 μg $ml^{-1}$; (3) bupivacaine with fentanyl 2 μg $ml^{-1}$; (4) bupivacaine with fentanyl 3 μg $ml^{-1}$; and (5) bupivacaine with fentanyl 4 μg $ml^{-1}$. The MLAC of bupivacaine were 0.069% w/v, 0.057% w/v, 0.048% w/v, 0.031% w/v and 0.015% w/v, respectively. We observed a reduction in MLAC of 18%, 31% ($P$=0.03%), 55% ($P$<0.0001) and 72% ($P$<0.0001) with fentanyl 1, 2, 3 and 4 μg $ml^{-1}$, respectively, demonstrating a significant negative linear trend ($P$<0.0001) with increasing fentanyl dose. The incidence of pruritus was increased significantly with fentanyl 4 μg $ml^{-1}$ ($P$=0.0015). Because of this, fentanyl 3 μg $ml^{-1}$ may be the optimal dose when the aim is bupivacaine sparing extradural analgesia during labour. (*Br. J. Anaesth.* 1997; **78**: 493–497).

**Key words**

Analgesia, obstetric. Analgesic techniques, extradural. Anaesthetics local, bupivacaine. Analgesics opioid, fentanyl.

The addition of extradural fentanyl to extradural bupivacaine in labouring women has been claimed to hasten onset of analgesia, increase its duration, diminish perineal discomfort[1] and reduce the amount of bupivacaine required to achieve comfort without motor block.[2 3] It improves maternal satisfaction[4] and may reduce the need for instrumental delivery.[5] Addition of fentanyl did not improve the quality of labour analgesia when given with plain bupivacaine at concentrations in excess of 0.2% w/v,[6] but permitted weaker concentrations to become effective in clinical practice.[7] This has prompted the use of dilute solutions of extradural bupivacaine in combination with opioids to achieve satisfactory analgesia but with a reduction in unwanted local anaesthetic effects such as motor block.[5] In this respect, extradural administration of sufentanil has been shown to reduce the requirement for bupivacaine in clinical practice by 20%,[8] but the relationship between varying doses of opioid and bupivacaine has never been adequately quantified.

Studies comparing efficacies of extradural analgesics have been hindered by ignorance of the relative potencies of the agents concerned, whether alone or in combination. Anaesthetic potencies of volatile agents have been described in terms of minimal anaesthetic concentration (MAC), and the same concept can be applied to extradural analgesics. An equianalgesic dose or concentration, or visual analogue pain score (VAPS) for both single agents and drug combinations would provide an extradural alternative to MAC. One such equianalgesic measure is the minimum local analgesic concentration (MLAC) of bupivacaine in labour.[9] This has provided a model which allows estimation of potency, and permits the bupivacaine sparing effect of successive doses of extradural opioid to be quantified. The aim of this study was to use this clinical model to access the ability of successive doses of extradural fentanyl to reduce the requirement for extradural bupivacaine, given to women in labour, using doses of fentanyl in the clinical range.

## Patients and methods

Our hospital Ethics Committee approved this study. After obtaining informed consent, we studied 223 women, ASA I or II, requesting extradural pain relief in the first stage of labour. We excluded those women in whom cervical dilatation exceeded 6 cm, and those who had received opioid or sedative drugs. Use of transcutaneous electrical nerve stimulator and Entonox before extradural request were not regarded as exclusion criteria.

Extradural blocks were sited in a standard manner. An i.v. infusion of 0.9% saline was started via a forearm cannula. The extradural space was found using a 17-gauge Tuohy needle, either at L2–3 or L3–4, in the sitting position. Loss of resistance to saline was used to identify the extradural space, limiting the injection to 2 ml in order to minimize dilution of local anaesthetic. For the purpose of the study, the test dose was omitted.

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The first administration of bupivacaine or bupivacaine–fentanyl was a freshly prepared syringe containing 20 ml of test solution given over 5 min. This was bupivacaine diluted with 0.9% saline to achieve the desired concentration at room temperature, with or without fentanyl, according to the groups below, which were studied in sequence.

### CONCENTRATIONS AND DOSES OF FENTANYL STUDIED

Forty women were included in each of five groups: (1) bupivacaine control, starting concentration was 0.1% w/v; (2) bupivacaine and fentanyl 1 $\mu$g ml$^{-1}$, starting concentration was 0.07% w/v; (3) bupivacaine and fentanyl 2 $\mu$g ml$^{-1}$, starting concentration was 0.06% w/v; (4) bupivacaine and fentanyl 3 $\mu$g ml$^{-1}$, starting concentration was 0.05% w/v; (5) bupivacaine and fentanyl 4 $\mu$g ml$^{-1}$, starting concentration was 0.04% w/v.

Doses of fentanyl were constant for each group. The first woman in each group received an arbitrarily chosen concentration of bupivacaine based on estimations of MLAC from preceding studies. Thereafter, the concentration of the test solution in each individual syringe was determined by the response of the previous patient to the higher or lower concentration in her test syringe, according to up and down sequential allocation. Routine maternal cardiovascular and fetal monitoring were performed.

### ASSESSMENT

The efficacy of the first dose was assessed using a 100-mm VAPS where 0 represented "no pain" and 100, "worst pain ever", at 0, 15 and 30 min after injection of the test solution (first dose). Three outcomes were possible.

#### *Effective*

This required that VAPS decreased to 10 mm or less at the height of contraction, within 15–60 min. This indicated the end of the study and directed a decrease of 0.01% w/v bupivacaine for the next woman.

#### *Ineffective*

This followed failure of the VAPS to reach 10 mm within 30 min of the test solution. If at 30 min the woman claimed satisfactory analgesia despite not reaching the VAPS target of 10 mm, the study period was extended to a maximum of 60 min. At 30 min, after failing to reach the VAPS target, rescue analgesia consisting of 0.25% w/v bupivacaine 12 ml was offered. After this, a reduction in VAPS to 10 mm or less indicated the end of the study and directed a 0.01% w/v bupivacaine increase for the next woman.

#### *Repeat*

Failure to achieve a VAPS of 10 mm, in the presence of pain outside T10–L1 distribution, or when the rescue bolus failed to achieve a VAPS of 10 mm or less, indicating either a source of pain other than the first stage of labour, or a technical failure of the extradural, directed that the same concentration be repeated for the next woman.

For all women, age, weight, height, gestation, parity, cervical dilatation, use of oxytocin and pruritus were recorded.

### STATISTICAL ANALYSIS

Patient and obstetric data were collected and are presented as mean (SD) and median (interquartile range) as appropriate. The median effective concentration was estimated from the up–down sequences using the formula of Dixon and Massey which enabled MLAC with 95% confidence interval to be derived.[10] The data were also subjected to Wilcoxon and Litchfield probit regression analysis as a back-up sensitivity test. Additional analyses included: Komolgorov–Smirnov test for Gaussian distribution, ANOVA, Bonferroni correction for multiple comparisons, post-test for linear trend, Kruskal–Wallis test, Fisher exact test and mid-$P$ value estimation for discrete data.[11 12] All analyses were carried out on two personal computers (Dell Dimension XPS P100c and Zenith Z-Star EX 486DX 50) using the following software: Microsoft Excel 5.0a for Windows, Statistical Package for the Social Sciences (SPSS) 6.1 for Windows, GraphPad Instat 2.05a for DOS and Pharmacologic Calculation System (PCS) 4.2 for DOS. Statistical significance was defined for an overall $\alpha$ error at the 0.05 level. All $P$ values were two-sided with multiple comparison corrections applied as appropriate.

Sample size estimations were based on the results of the first MLAC studies which showed the MLAC of bupivacaine to be 0.065% (SD 0.037%).[9] A conservative $\alpha$ error of 0.01 was applied to allow for multiple comparisons. Power was given at 0.9, with the minimum significant difference a 50% reduction in the MLAC of bupivacaine by fentanyl. It was then estimated that a minimum of 39 women would be required per group.

## Results

There were no significant differences in patient or obstetric characteristics between the groups (table 1).

There were significant dose-dependent reductions in the MLAC of bupivacaine with fentanyl 2 $\mu$g ml$^{-1}$ ($P=0.03$), 3 $\mu$g ml$^{-1}$ ($P<0.0001$) and 4 $\mu$g ml$^{-1}$ ($P<0.0001$) compared with the bupivacaine control (table 2). This was demonstrated also by a significant negative linear trend for the MLAC of bupivacaine ($P<0.0001$) with increasing fentanyl doses.

Sequences of effective and ineffective analgesia are shown in figure 1.

There were significant reductions in the repeat rates with fentanyl 2 $\mu$g ml$^{-1}$ ($P=0.038$), 3 $\mu$g ml$^{-1}$ ($P=0.038$) and 4 $\mu$g ml$^{-1}$ ($P=0.01$) compared with bupivacaine control (table 3).

Pruritis was increased significantly by fentanyl

*Table 1* Patient and obstetric data. Results are expressed as mean (SD or range), median [interquartile range] and count as appropriate. VAPS=Visual analogue pain score.

| | Bupivacaine | Fentanyl 1 $\mu$g ml$^{-1}$ | Fentanyl 2 $\mu$g ml$^{-1}$ | Fentanyl 3 $\mu$g ml$^{-1}$ | Fentanyl 4 $\mu$g ml$^{-1}$ |
|---|---|---|---|---|---|
| Age (yr) | 27.5 (18–40) | 27.2 (17–40) | 25.4 (17–38) | 27.8 (19–37) | 26.7 (17–39) |
| Height (cm) | 162 (6.5) | 163 (6.0) | 162 (4.5) | 163 (6.6) | 163 (7.2) |
| Weight (kg) | 76 (12.2) | 79 (13.0) | 73 (10.6) | 72 (14.1) | 74 (15.3) |
| Gestation (weeks) | 40 [40–41] | 40 [39–40] | 40 [39–40] | 39 [38–40] | 40 [39–40] |
| Cervical dilatation (cm) | 3 [3–4] | 3 [3–4] | 3 [3–4] | 4 [3–5] | 4 [3–4] |
| Parity | 0 [0–1] | 0 [0–1] | 0 [0–1] | 0 [0–1] | 0 [0–1] |
| Nulliparous/multiparous | 27/13 | 28/12 | 28/12 | 27/13 | 26/14 |
| Initial VAPS (mm) | 75 [61–90] | 80 [66–91] | 65 [60–81] | 66 [51–77] | 68 [50–88] |

*Table 2* MLAC of bupivacaine and fentanyl concentrations, compared with MLAC of control. MLAC = Minimum local analgesic concentration using the method of Dixon and Massey.[10] $P$=$P$ value (95% confidence interval) using modified $t$ tests *vs* MLAC of control. *$P$=$P$ value (95% confidence interval) with Bonferroni correction

| | MLAC | $P$ | $P$* |
|---|---|---|---|
| Bupivacaine | 0.069 (0.057–0.080) | | |
| Fentanyl 1 $\mu$g ml$^{-1}$ | 0.057 (0.047–0.066) | 0.14 (−0.003–0.027) | 0.52(−0.008–0.032) |
| Fentanyl 2 $\mu$g ml$^{-1}$ | 0.048 (0.037–0.059) | 0.008 (0.006–0.036) | 0.03 (0.0013–0.041) |
| Fentanyl 3 $\mu$g ml$^{-1}$ | 0.031 (0.017–0.045) | <0.0001 (0.022–0.054) | <0.0001 (0.018 to 0.058) |
| Fentanyl 4 $\mu$g ml$^{-1}$ | 0.015 (0.004–0.025) | <0.0001 (0.039–0.069) | <0.001 (0.035–0.073) |

*Table 3* Distribution of repeats. **$P$=<0.01 compared with bupivacaine control

| Bupivacaine %w/v | Bupivacaine | Fentanyl 1 $\mu$g/ml$^{-1}$ | Fentanyl 2 $\mu$g/ml$^{-1}$ | Fentanyl 3 $\mu$g/ml$^{-1}$ | Fentanyl 4 $\mu$g/ml$^{-1}$ |
|---|---|---|---|---|---|
| 0.1 | 1 | | | | |
| 0.09 | 1 | | | | |
| 0.08 | 2 | 1 | | | |
| 0.07 | 2 | | | | |
| 0.06 | 3 | 2 | | | |
| 0.05 | 3 | 1 | 1 | 1 | |
| 0.04 | 1 | | | | |
| 0.03 | | 1 | 1 | | |
| 0.02 | | | | | |
| 0.01 | | | | | 1 |
| 0 | | | | 1 | |

*Table 4* Incidence of pruritus compared with bupivacaine control. *Bonferroni corrected $P$=0.0015

| | Pruritus | $P$ |
|---|---|---|
| Bupivacaine | 0 | |
| Fentanyl 1 $\mu$g/ml$^{-1}$ | 2 | 0.49 |
| Fentanyl 2 $\mu$g/ml$^{-1}$ | 2 | 0.49 |
| Fentanyl 3 $\mu$g/ml$^{-1}$ | 4 | 0.12 |
| Fentanyl 4 $\mu$g/ml$^{-1}$ | 11 | 0.0004* |

4 $\mu$g ml$^{-1}$ ($P$=0.0015) compared with the bupivacaine control (table 4).

## Discussion

We have shown that the addition of extradural fentanyl to extradural bupivacaine in labour produced a dose-dependent reduction in the requirements for bupivacaine. Significant reductions were obtained with fentanyl 2, 3 and 4 $\mu$g ml$^{-1}$ (40 $\mu$g, 60 $\mu$g and 80 $\mu$g). The latter dose, however, caused a marked incidence of pruritus (23%). Although fentanyl 4 $\mu$g ml$^{-1}$ proved to be the most effective in terms of bupivacaine sparing, the cost in side effects may well make a dose of 3 $\mu$g ml$^{-1}$ the choice for clinical practice. Doses in excess of 4 $\mu$g ml$^{-1}$ were not studied because of the increasing incidence of pruritus. Eight patients in the 4-$\mu$g ml$^{-1}$ group received test solutions that did not contain local anaesthetic. Further reductions in MLAC could be achieved only by an increase in opioid only recipients, up to a maximum number of study patients. Clearly, at a dose somewhere in excess of 4 $\mu$g ml$^{-1}$, clinically important reductions in bupivacaine concentration would become hard to achieve. Comfort in labour has been achieved with fentanyl alone.[2]

### TEST DOSE

In common with others, we did not use a test dose.[7] Because of its sensitivity and specificity in the detection of i.v. injection,[13] we used 2% w/v lignocaine 1 mg kg$^{-1}$ as an extradural test dose. Our earlier study[9] suggested that this dose can have a therapeutic effect. The MLAC of lignocaine was 0.37% w/v, which corresponds to a median effective dose of 74 mg. It is clear that a test dose of this magnitude might interact with the efficacy of subsequently administered extradural analgesics. We have found in our own clinical practice that

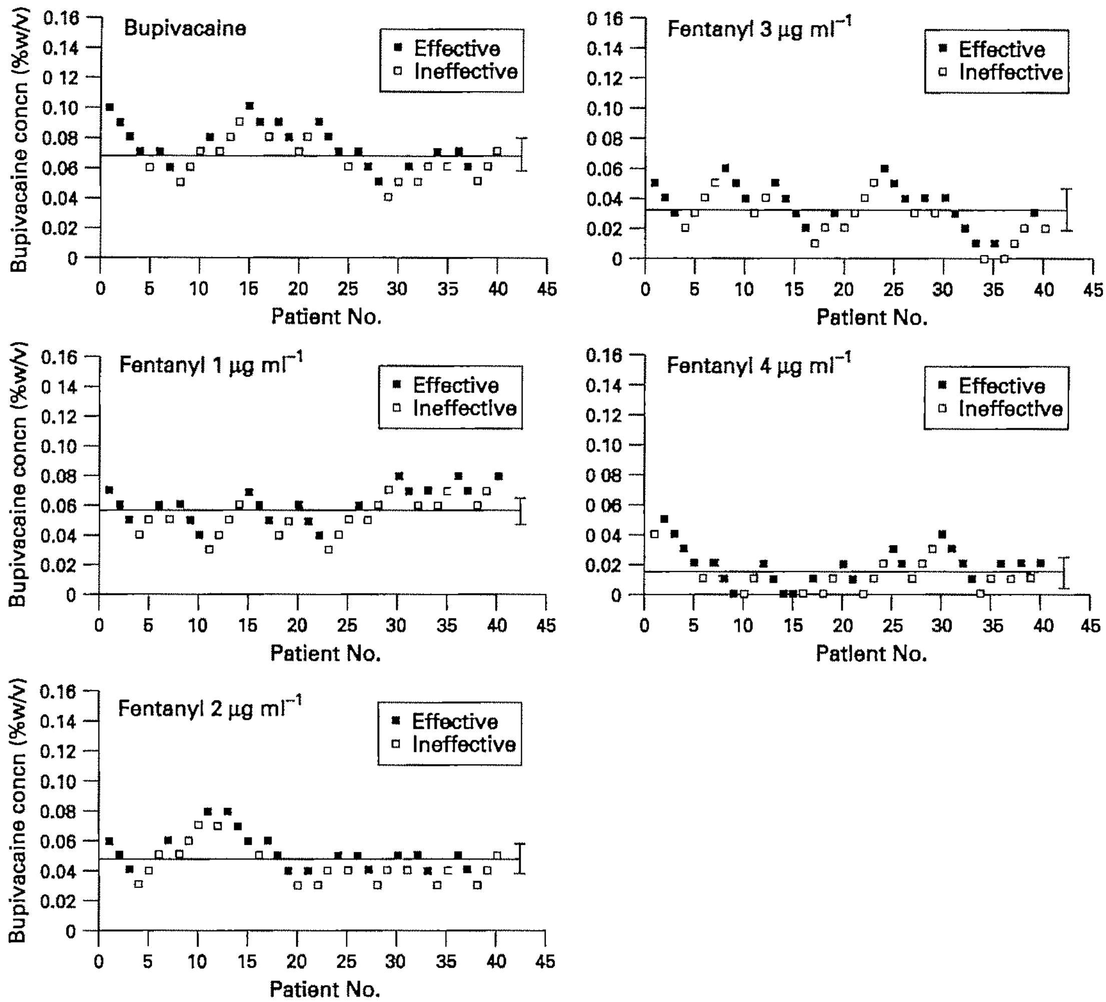

*Figure 1* EC$_{50}$ of bupivacaine, fentanyl 1, 2, 3 and 4 µg ml$^{-1}$, as determined by the technique of up-down sequential allocation. Error bars represent 95% confidence interval. Testing interval was 0.01% w/v.

2% w/v extradural lignocaine 1 mg kg$^{-1}$ achieves satisfactory comfort in approximately 40% of women, and its inclusion would have interfered with interpretation.

## TARGET VAPS

Determining the EC$_{50}$ for an analgesic implies that analgesia fails in 50% of the sample. Brownridge has shown that in labour, a VAPS of 30 mm or less corresponds to comfort.[14] Sensitive to the request for pain relief, we chose as our target a VAPS of 10 mm. While making the required degree of analgesia more exacting, it ensured that approximately 30% of the "ineffective" solutions produced VAPS below Brownridge's comfort line.

## RESCUE

After an "ineffective" solution it was important that pain was abolished rapidly. There was also a concern that failure to meet the target VAPS might be caused by a technical problem of the extradural or by pain from a source outside the normal distribution of first stage pain, and not a genuine therapeutic failure. To achieve comfort rapidly, and simultaneously demonstrate that the extradural was capable of analgesia with bupivacaine alone, the rescue was devised in a volume, and at a concentration that we considered would meet these aims unequivocally. Milligan and colleagues showed that 0.25% w/v bupivacaine 12 ml produced analgesia to at least the T10 dermatome in 80 women.[15]

## REPEATS

When the test solution produced analgesia in a first stage distribution, but the VAPS exceeded 10 mm because of persistent, generally perineal, discomfort, we chose to repeat that concentration. While there was a subjective element to this assessment, it was necessary to ensure that only the concentration of local anaesthetic decided therapeutic efficacy. The degree of subjectivity in making this assessment influenced directly the number of repeats. Any bias this introduced operated equally for all groups as the investigators were blinded to the concentrations used throughout the studies. The addition of fentanyl 2 µg ml$^{-1}$ or greater reduced significantly the number of instances when therapeutic failure was in doubt. Failure of rescue indicated the need to resite the extradural, and necessitated a repeat of the test solution in the subsequent woman.

STATISTICAL ANALYSIS

The formula of Dixon and Massey was used to derive MLAC and 95% confidence interval from the results of sequential allocation.[9] Regression techniques have been used by other workers to analyse similar up–down data, so we applied probit regression as a back-up sensitivity test.[16] We believe that the former test is more appropriate even though the latter is generally less conservative with the data. Regression analysis is usually applied to randomly rather than sequentially allocated data. This is in keeping with theoretical arguments that the observations in up–down allocation are not completely independent and that the possibility of heteroscadesis is not necessarily examined. In stating this, however, we do not wish to be critical of other workers as the two analyses return reasonable approximations to each other.

The power of these studies (1.0, range 0.36–1.0 for the observed results) suggests overestimation of the required sample size to find significance for a 50% reduction in the MLAC of bupivacaine by fentanyl. This was probably caused by an initial overestimation of the SD.

We believe that comparisons of arbitrarily chosen analgesic recipes are an inappropriate method of dose finding in labour and that there is a need to create a benchmark for extradural analgesics. A suggestion that this can be done with equimolar solutions[17] has some value, but clinical practice requires a benchmark for analgesia. Estimation of equianalgesia (MLAC) allows the contribution of components of a drug cocktail to be quantified, and doses adjusted for best effect. When comparative studies are performed with equianalgesic combinations, best solutions are identified, not in terms of analgesia, but in terms of undesirable effects

In summary, we have shown that extradural fentanyl reduced the requirement for extradural bupivacaine during the first stage of labour in a dose-dependent manner. We have also shown that by combining it with bupivacaine, the number of blocks deemed to be deficient in spread (repeats) was reduced significantly. By inference, increasing doses of extradural fentanyl should permit greater motor sparing, but this requires further study. Fentanyl 4 μg ml$^{-1}$, while producing the greatest depression of MLAC (78%), produced a significant amount of pruritus, and for this reason fentanyl 3 μg ml$^{-1}$ may represent the optimum dose.

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*British Journal of Anaesthesia* 1997; 78: 498–501

# Combined spinal–extradural anaesthesia for preterm and term Caesarean section: is there a difference in local anaesthetic requirements?

K. S. JAMES, E. MCGRADY AND A. PATRICK

## Summary

In a non-blinded observational study, we have tested the null hypothesis that there is no difference in local anaesthetic requirements for subarachnoid anaesthesia between women presenting for Caesarean section at term or preterm (38–42 and 28–35 weeks' gestation, respectively). Using a combined spinal–extradural technique, 2.25 ml of 0.5% hyperbaric bupivacaine was given, in the sitting position, to 50 women presenting for Caesarean section. In 21 of 25 preterm women, adequate sensory block for surgery did not develop ($P<0.001$) and they required supplementary extradural local anaesthetic (median 8 ml of 2% lignocaine with 1:200 000 adrenaline (interquartile range 4–12 ml)); preterm women not requiring extradural supplementation were at the upper end of the gestational range. There was a strong linear correlation between increasing gestation and block height in the preterm group (Spearman rank correlation coefficient=0.74; 95% confidence intervals 0.49, 0.88). All women in the term group developed adequate anaesthesia with the subarachnoid dose alone. Onset of anaesthesia was slower in the preterm group (median 15 *vs* 5 min) with a lower incidence of hypotension ($P=0.0005$). (*Br. J. Anaesth.* 1997; **78**: 498–501).

**Key words**
Anaesthesia, obstetric. Anaesthetic techniques, extradural. Anaesthetic techniques, subarachnoid. Anaesthetics local, bupivacaine.

In the UK, the Caesarean section rate is rising with a disproportionate increase in the number of preterm Caesarean sections.[1 2] In 1995 just over 11% of Caesarean sections were performed on mothers at less than 36 weeks' gestation[1 2] and improving obstetric and neonatal management allows a better prognosis for these babies. Babies have better Apgar and neurobehavioural scores when mothers have a regional rather than a general anaesthetic[3–5] and as preterm babies are already compromised, it seems sensible to use an anaesthetic technique which avoids giving depressant drugs to both mother and fetus. Despite this, a large proportion (39%)[6] of mothers receive a general anaesthetic for Caesarean delivery which may be related to the fact that standard textbooks give little guidance on the management of regional anaesthesia for preterm Caesarean section.

Pregnant women at term require less subarachnoid local anaesthetic than non-pregnant women to achieve a given sensory block.[7–9] While it has been suggested that preterm women require the same local anaesthetic dose as those at term,[10 11] our own clinical observations suggested that preterm women needed larger doses to achieve adequate sensory block for surgery.

The aim of this study was to assess if a standard subarachnoid dose of local anaesthetic produced similar sensory block levels in women at term and preterm (38–42 and 28–35 weeks' gestation, respectively), presenting for Caesarean section, and to test the null hypothesis that there is no difference in local anaesthetic requirements between these groups.

## Patients and methods

After obtaining hospital Ethics Committee approval, we studied 50 women who gave written informed consent. We used 25 women as controls, presenting for elective Caesarean section at term, and 25 women required delivery by Caesarean section between 28 and 35 weeks' gestation.

With the mother in a sitting position, a combined spinal–extradural kit was used with a standard 16-gauge Tuohy needle and a 117-mm long 26-gauge pencil-point spinal needle, designed to pass through the lumen of the extradural needle after location of the extradural space, and which can extend up to 12 mm beyond the end of the extradural needle (Portex Ltd). After a preload of 15 ml $kg^{-1}$ of crystalloid solution the extradural space was located with the 16-gauge Tuohy needle using loss of resistance to saline and the 26-gauge pencil-point needle passed through the lumen of the Tuohy needle into the subarachnoid space. When CSF was seen in the hub of the needle, 2.25 ml of 0.5% hyperbaric bupivacaine was injected over 30 s without barbotage. The spinal

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needle was then withdrawn, an extradural catheter inserted and secured, and the mother immediately placed supine with 20° left lateral tilt.

Sensory block height was measured 3 min after subarachnoid injection and then at 2-min intervals until it had stopped rising. As we were performing repeated measurements, we chose to measure block height with loss of cold sensation. A block to T4 was considered necessary before allowing surgery to start. Assessment of the block to pinprick was made at this time and anaesthetic (feels nothing) and analgesic (aware of pinprick but not sharp) block heights were recorded. If the subarachnoid block stopped increasing (three consecutive block measurements without change) before it reached T4, supplementary extradural local anaesthetic was added. We injected 2 ml of 2% lignocaine with adrenaline 1:200 000 for each dermatome level between the maximum height of the subarachnoid block and T4.

Block height after subarachnoid injection alone, supplementary extradural local anaesthetic requirements, maximum block height, time taken to reach T4 and the incidence of hypotension (a decrease in systolic pressure to <70% of pre-spinal level) were recorded. Statistical analysis was performed with Minitab for Windows version 9.2 using the chi-square test, Mann–Whitney *U* test and Spearman rank correlation as appropriate.

Hospital clinical audit showed that 99% of women presenting for elective Caesarean section at term achieved a block to T4 with 2.25 ml of 0.5% hyperbaric bupivacaine. We can assume that if only 70% of preterm women achieved a suitable block this would be clinically important (i.e. 30% failure rate). As the outcome is either success or failure the statistical test is the difference in two binomial proportions. With a significance level of $P<0.01$ and a power of 0.99, the sample size required for each group (term and preterm) was 21. We studied 25 patients in each group in case data were lost.

*Table 1* Patient data (median (interquartile range)) (*P* values, Mann–Whitney *U* test

| | Preterm group ($n=25$) | Term group ($n=25$) | *P* |
|---|---|---|---|
| Age (yr) | 30 (25–33.5) | 32 (29–36) | 0.137 |
| Gestation (weeks) | 32 (29.5–34) | 38 (38–39) | <0.001 |
| Height (cm) | 161 (157–164) | 161 (156–166) | 0.85 |
| Weight (kg) | 72 (67–78) | 75 (70.5–80.5) | 0.28 |

*Table 2* Number of preterm women at each gestational age

| Gestational age (weeks) | No. of women |
|---|---|
| 28 | 3 |
| 29 | 3 |
| 30 | 2 |
| 31 | 4 |
| 32 | 2 |
| 33 | 2 |
| 34 | 6 |
| 35 | 3 |

## Results

With the exception of gestational age, both groups were similar (table 1). The numbers of preterm women at each week of gestational age are shown in table 2.

There was a significant difference between the term and preterm groups in maximum block height after subarachnoid injection ($P<0.001$). All women at term developed an anaesthetic block to T4, but 84% of preterm women failed to achieve a T4 block (table 3).

There was a strong linear correlation between increasing gestational age and block height produced with subarachnoid local anaesthetic alone (Spearman rank correlation=0.74: 95% confidence intervals 0.49, 0.88) (fig. 1).

The four preterm women who developed a block to T4 were at the upper end of the preterm gestational age limit; three at 35 weeks' and one at 34

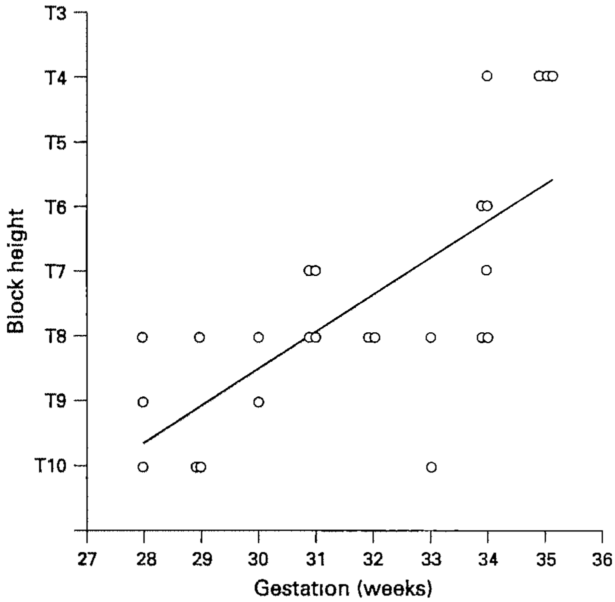

*Figure 1* Correlation between maximum sensory block height achieved with subarachnoid anaesthesia alone and gestational age.

*Table 3* A: Sensory block to T4 with subarachnoid local anaesthetic alone (*P* value. chi square=36.207, df 1, $p<0.001$), B: time to T4 and maximum sensory block height after addition of extradural local anaesthetic if required (median (interquartile range)) (*P* values: Mann–Whitney *U* test); C: hypotension (*P* value: chi square=12.00, df=1, $P=0.0005$)

| | | Preterm group ($n=25$) | Term group ($n=25$) | *P* |
|---|---|---|---|---|
| A | block to T4 with subarachnoid local anaesthetic alone (No. of women) | 4 | 25 | <0.001 |
| B | Time to T4 (min) | 15 (11–17) | 5 (5–7) | <0.001 |
| | Max. block height | T4 (T4–T3) | T3 (T4–T2) | 0.0008 |
| C | Hypotension (No. of patients) | 4 | 16 | 0.0005 |

weeks' gestation. Five other woman at 34 weeks' gestation did not develop a block to T4 and required supplementary extradural local anaesthetic. All other preterm women were less than 34 weeks' gestation and all required supplementary extradural local anaesthetic.

The median time to achieve a block to T4 was 5 min in the term group and 15 min in the preterm group ($P<0.001$) (table 3). The maximum time taken for any patient to develop a T4 block in the preterm group was 22 min.

Maximum block heights were higher in the term group receiving subarachnoid local anaesthetic alone compared with the preterm group after addition of supplementary extradural local anaesthetic (medians T3 and T4, respectively) ($P=0.0008$) (table 3).

There was significantly less hypotension in the preterm group, with only four women with a 30% decrease in arterial pressure ($P=0.0005$) (table 3).

## Discussion

Our results confirmed that, using the technique described, a standard subarachnoid dose of local anaesthetic, appropriate for women at term, failed to reliably provide adequate anaesthesia for preterm women requiring Caesarean section. All women with a gestational age less than 34 weeks required supplementary extradural local anaesthetic to achieve sensory block to T4.

Why do preterm women require more local anaesthetic? It is known that women at term require less local anaesthetic than non-pregnant women, and this seems to be related to physiological and hormonal changes in pregnancy. It is known that in late pregnancy the gravid uterus compresses the inferior vena cave, impairing venous return from the legs and pelvis,[8] and it has been assumed that as the collateral circulation includes the extradural veins, resultant distension of extradural veins effectively reduces the volume of both the extradural and subarachnoid spaces, altering the distribution of drugs injected into the CSF.[8 9] This has been confirmed by Hirabayashi and co-workers, who have demonstrated, using magnetic resonance images, that the extradural venous plexus is engorged in the supine parturient compared with the same women before pregnancy.[12] The engorged extradural veins also displace the dura, thereby decreasing the volume of the subarachnoid space. In addition, increased CSF prostaglandin concentrations in pregnancy increase the sensitivity of nerves to local anaesthetics,[13 14] and this may also contribute to a reduction in local anaesthetic requirements.

Preterm women, in late second or early third trimesters, with a smaller uterus than those at term, presumably have less inferior vena caval compression, less collateral flow through the extradural venous plexus and therefore larger extradural and subarachnoid volumes. In addition, the effect of prostaglandins on nerves may be related not only to increased prostaglandin concentrations but also to the duration of exposure to the increased concentration, with preterm women having had shorter exposure times.[15]

We induced subarachnoid anaesthesia with women in the sitting position and chose a 2.25 ml (11.25 mg) dose of hyperbaric bupivacaine as 2 ml (10 mg) has been shown to be inadequate in 37.5% of term women,[16] and a single space combined spinal–extradural technique was used so that women could receive supplementary extradural local anaesthetic if required. We found that this technique provided a gradual onset of anaesthesia with a reliable block height (no patient developed an inappropriately high block) and minimal hypotension, which should be beneficial to the compromised preterm fetus. Although using extradural 2% lignocaine and adrenaline 1:200,000 minimized the onset time of extradural block,[17] as expected it took significantly longer to achieve a T4 block in the preterm group. The difference in median times to T4 was 10 min, unlikely to be clinically important in most cases. In keeping with a slower onset of sensory block, the incidence of hypotension was significantly lower in the preterm group ($P=0.0005$).

We attempted to identify factors which might reliably predict sensory block height after subarachnoid injection and found a strong linear correlation between increasing gestational age and higher blocks (Spearman rank correlation=0.74: 95% CI 0.49, 0.88). Given why we believe preterm women need more local anaesthetic, it would seem logical that there would be some association between uterine size and local anaesthetic requirements. We assessed uterine size by measuring fundal height taken from the symphysis pubis to the fundus and found a correlation between gestational age and fundal height (Spearmann rank correlation=0.55, 95% CI 0.20, 0.77) and between fundal height and block achieved with subarachnoid local anaesthetic (Spearman rank correlation=0.85, 95% CI 0.68, 0.93) (fig. 2). Although uterine size may be more important than gestational age in predicting dose requirements it is difficult to measure accurately.

In summary, we have shown that subarachnoid

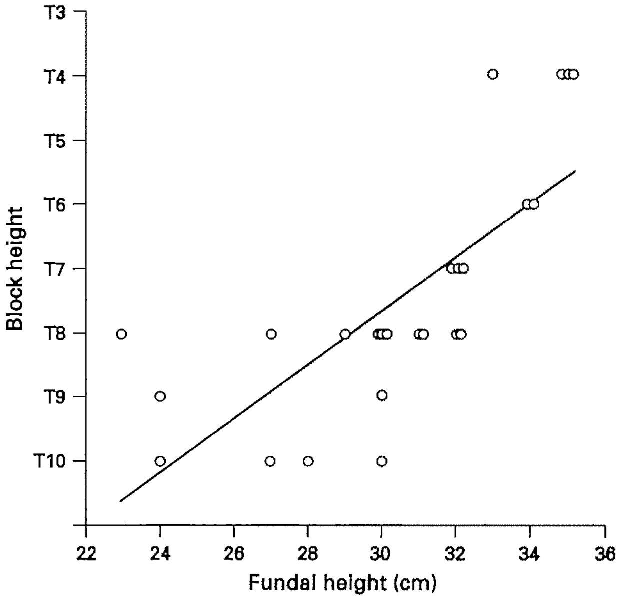

*Figure 2* Correlation between maximum sensory block height achieved with subarachnoid anaesthesia alone and fundal height.

injection of 2.25 ml of hyperbaric bupivacaine, with women in a sitting position, failed to provide adequate anaesthesia for Caesarean section in 84% of preterm women and we can reject the null hypothesis that subarachnoid local anaesthetic requirements in these two groups are the same. Preterm women required more local anaesthetic and there was a strong correlation between increasing gestation and higher block for a given dose of local anaesthetic. However, it is difficult to predict accurately the dose for an individual preterm patient and the combined spinal–extradural technique should be used when time allows, as this produces reliable and stable anaesthesia with little hypotension. If urgent Caesarean section is required and a single dose subarachnoid anaesthetic is planned, a larger dose of local anaesthetic should be used.

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# Effect of lignocaine and pH on propofol-induced pain

M. ERIKSSON, S. ENGLESSON, F. NIKLASSON AND P. HARTVIG

## Summary

Propofol has the disadvantage of pain on injection. A higher partition of propofol in the aqueous phase of the preparation causes a higher incidence of pain on injection while addition of 1% lignocaine to propofol reduces pain. The low concentration of this local anaesthetic and the rapid pain relief observed indicates that mechanisms other than local anaesthesia are involved, that is change in pH. We performed a clinical study to investigate the influence of lignocaine and pH on pain during injection of 1% Diprivan. Ten parts of 1% Diprivan were mixed with one part of saline, 1% lignocaine or hydrochloric acid to achieve the same pH as that after addition of lignocaine. Diprivan 1% mixed with 1% lignocaine and with hydrochloric acid gave mean pain ratings (1–10) of 0.32 (SD 0.75) (*n*=25) and 0.88 (1.30) (*n*=24), respectively. These ratings were significantly lower than ratings after injection of a saline–Diprivan mixture (2.18 (2.06), *n*=22). The pH of the 1% Diprivan formulation decreased after mixing with 1% lignocaine. The concentration of propofol in the aqueous phase was lower when 1% Diprivan was mixed with 1% lignocaine (0.376 g $\text{litre}^{-1}$) or HCl (0.392 g $\text{litre}^{-1}$) compared with 1% Diprivan and saline (0.476 g $\text{litre}^{-1}$) mixed in the same proportion. Thus pH changes may modify propofol-induced pain on injection by a mechanism different from the effect of the local anaesthetic on the vascular endothelium. Our findings may explain why lignocaine mixed with propofol causes less pain than injection of lignocaine followed by propofol. (*Br. J. Anaesth.* 1997; **78**: 502–506).

**Key words**
Formulations, propofol. Formulations, pH. Pain, injection. Anaesthetics i.v., propofol. Anaesthetics local, lignocaine.

Propofol (Diprivan; 2,6-diisopropyl phenol) causes pain on i.v. administration.[1] Initially it was formulated in Cremophor EL which may increase the risk of anaphylactic reactions and as a consequence propofol was formulated as an aqueous emulsion in soybean oil.[2 3] Dissolving diazepam and etomidate in soybean oil (Intralipid) almost abolished the pain associated with their injection[4 5] but the same is not true for propofol although pain is known to be related to the aqueous concentration of propofol in the emulsion.[6 7] Pain after injection of propofol is thought to be caused by direct stimulation of venous nociceptive receptors or free nerve endings, the nerve impulse being transmitted by thinly myelinated A delta fibres.[8] If a local anaesthetic affects these nerve cells it must penetrate the cell membrane in its uncharged form and is then converted to its ionized form which anaesthetizes intracellular receptors.

Pain on injection induced by propofol has been found to be reduced by a preceding injection of lignocaine.[2] A direct effect of local anaesthetics on vascular smooth muscle has been suggested.[9] Comparisons between the efficacy of lignocaine injected before propofol and of mixtures of lignocaine and propofol injected simultaneously have shown that the latter causes less pain on injection.[3 10] Knowledge of the mechanism by which a small amount of lignocaine counteracts pain caused by subsequent injection of propofol is valuable. Small quantities of local anaesthetic can reduce such pain at the injection site, but also the pain observed at more proximal sites. This suggests an effect of lignocaine on propofol-induced pain on injection separate from its local anaesthetic action.

It is not clear how such low concentrations of lignocaine mixed with propofol (e.g. 1:10) and thereby diluted to a 0.1% solution almost instantaneously prevents propofol-induced pain on injection. Alternative explanations for the efficacy of lignocaine on injection pain caused by propofol include: lignocaine hydrochloride is a weak free base–cation solution which, when exposed to lipids, liberates protons as the free base dissolves in the lipids, thereby decreasing the pH of the mixture; the lower pH produced after mixing lignocaine with Diprivan reduces the concentration of propofol anions as propofol is a weak acid with a $pK_a$ of 11. The net effect would be an increased amount of propofol which migrates into the lipid phase. Such an effect would result in reduced pain on injection.[7 11]

In order to determine if the change in pH achieved by adding lignocaine to the Diprivan solution or the local anaesthetic effect of lignocaine is the main mechanism for reduction of pain on injection, we observed the responses of solutions in which the pH

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change was created by lignocaine or by addition of hydrochloric acid. Diprivan 1% mixed with lignocaine, hydrochloric acid or saline, all three with the same degree of dilution, were prepared and tested in patients. Chemical analysis was also performed whereby pH titrations were made with 1% Diprivan mixed with increasing amounts of lignocaine or hydrochloric acid. These titrations were also made with 10% and 20% Intralipid solutions, the former corresponding to the emulsion used in 1% Diprivan.

## Patients and methods

### PAIN DETERMINATION

After obtaining approval from the local Ethics Committee of the University of Uppsala and the Swedish Medical Products Agency, we studied 44 patients (18 males), ASA I or II, undergoing elective ENT surgery. All patients gave informed consent to participate in this study. Mean age was 43 (range 18–72) yr. Patients were requested to name which of two propofol injections, one in each hand, at its maximum caused most discomfort and in addition to grade the pain, where "0"=no pain, "1"=hardly recognizable and "10"=extreme pain. Premedication was with ketobemidon (Ketogan Novum; an analogue to morphine) 2.5–5 mg and atropine 0.5 mg or glycopyrronium (Robinul) 0.2 mg injected i.m. 30 min before induction of anaesthesia. A 20-gauge i.v. cannula was inserted in a dorsal vein of each hand. Coded ampoules containing 2 ml of either sterile 1% lignocaine, sterile hydrochloric acid 0.064 mol $litre^{-1}$ or saline were prepared in advance. No efforts were made to stratify the material. Diprivan 1% (10 ml) at room temperature was mixed with 1 ml of the contents of a randomly chosen ampoule. All mixtures were prepared immediately before injection and all injections were made in a double-blind manner. Two millilitres of the mixtures were injected simultaneously in each cannula over a period of 25–30 s.

### DRUGS AND EQUIPMENT

We used propofol (1% Diprivan; Zeneca AB, Sweden), lignocaine (1% Xylocain; Astra AB, Sweden) and a soybean oil emulsion (Intralipid; Kabi Pharmacia AB, Sweden), similar to the solvent in which propofol is emulsified. pH values of each compound and the mixtures were determined with a pH meter (PHM 92, Radiometer, Copenhagen, Denmark) calibrated at pH values of 4.00 and 7.00. All experimental procedures were performed at least in duplicate.

Analysis of propofol and lignocaine concentrations was performed by liquid chromatography of the aqueous phases obtained by ultracentrifuging the Diprivan preparations. These analyses were performed by Dr Björn Norlander, Department of Clinical Pharmacology, University of Linköping.

Diprivan 1% was mixed randomly (10+1) with 1% lignocaine, hydrochloric acid 0.0064 mol $litre^{-1}$ or saline and administered into surgical patients in a double-blind, randomized manner.

The following chemical experiments and titrations were performed with Diprivan and Intralipid mixed with either lignocaine, hydrochloric acid or saline: pH was measured in 1% Diprivan and in the commercially available 1% and 4% solutions of lignocaine. pH was also measured in the mixture (10:1) of 1% Diprivan and 1% lignocaine. A titration was also made with increasing amounts of lignocaine (10:2, 10:4) and the pH of each mixture measured. A new titration with 4% lignocaine was also made (10:0.25, 10:0.5, 10:1, 10:2, 10:4) which added the same amount of lignocaine to 1% Diprivan.

### STATISTICAL ANALYSIS

Analysis of variance was used to test the hypothesis of no difference between treatment groups. If this hypothesis was rejected at the 5% level using the *F* test, least-square means were calculated and compared between each pair of treatment groups. The magnitude of the differences was explored by use of 95% confidence limits. Results are expressed as mean (SD).

## Results

### *IN VIVO* EXPERIMENTS

Pain rating after administration of 10 parts of 1% propofol mixed with one part of either 1% lignocaine, hydrochloric acid 0.0064 mol $litre^{-1}$ or saline, respectively, was determined verbally. The highest pain rating was observed in the group of patients that received 1% propofol mixed with saline (table 1).

The discomfort caused by injection of 1% propofol mixed with saline was significantly higher than

*Table 1* Pain on injection caused by propofol 10 mg $ml^{-1}$ mixed with saline, hydrochloric acid 0.0064 mol $litre^{-1}$ or 1% lignocaine in a ratio of 10+1

| | Propofol+ saline | Propofol+ HCl | Propofol+ lignocaine |
|---|---|---|---|
| *n* | 22 | 24 | 25 |
| Mean | 2.18 | 0.88 | 0.32 |
| SD | 2 06 | 1.30 | 0.75 |
| LS mean | 2 18 | 0.88 | 0.32 |

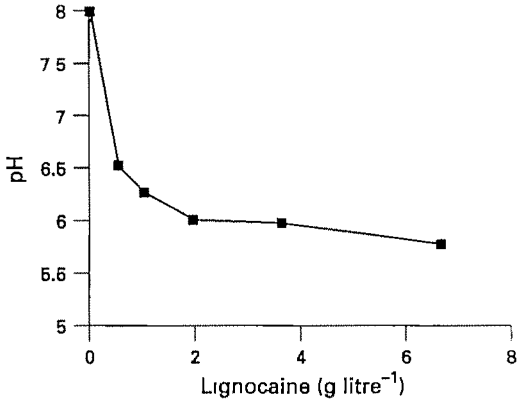

*Figure 1* Effect on pH of increasing amounts of lignocaine added to 1% Diprivan.

*Table 2* Differences between groups of patients given propofol 10 mg ml$^{-1}$ mixed with saline, hydrochloric (HCl) acid 0.0064 mol litre$^{-1}$ or 1% lignocaine in a ratio of 10+1

| | Difference | 95% Confidence interval | *P* |
|---|---|---|---|
| Propofol+HCl *vs* propofol+lignocaine | 0.5550 | −0.4322, 1.5422 | 0.1824 |
| Propofol+saline *vs* propofol+HCl | 1.3068 | 0.2872, 2.3264 | 0.0031 |
| Propofol+saline *vs* propofol+lignocaine | 1.8616 | 0.8520, 2.8716 | <0.0001 |

*Table 3* Effect on pH in a commercial propofol emulsion (Diprivan) by increasing volumes and concentrations of lignocaine

| Preparation | pH |
|---|---|
| 1% Lignocaine | 6.75 |
| 1% Propofol in Diprivan | 7.97–8.02 |
| 1% Diprivan 2 ml+1% lignocaine 0.1 ml | 6.57 |
| 1% Diprivan 2 ml+1% lignocaine 0.2 ml | 6.32 |
| 1% Diprivan 2 ml+1% lignocaine 0.4 ml | 6.14 |
| 4% Lignocaine | 6.59 |
| 1% Diprivan 2 ml+4% lignocaine 0.025 ml | 6.52 |
| 1% Diprivan 2 ml+4% lignocaine 0.05 ml | 6.27 |
| 1% Diprivan 2 ml+4% lignocaine 0.1 ml | 6.09–6.01 |
| 1% Diprivan 2 ml+4% lignocaine 0.2 ml | 5.89 |
| 1% Diprivan 2 ml+4% lignocaine 0.4 ml | 5.78 |

*Table 4* Effect on pH of increasing volumes and concentrations of lignocaine on a commercial 10% and 20% soybean emulsion (Intralipid)

| Preparation | pH |
|---|---|
| 10% Soybean emulsion | 7.56 |
| 10% Soybean emulsion 2 ml+4% lignocaine 0.1 ml | 6.15 |
| 10% Soybean emulsion 2 ml+4% lignocaine 0.2 ml | 6.05 |
| 10% Soybean emulsion 2 ml+4% lignocaine 0.4 ml | 6.03 |
| 20% Soybean emulsion | 7.54 |
| 20% Soybean emulsion 2 ml+4% lignocaine 0.1 ml | 5.93 |
| 20% Soybean emulsion 2 ml+4% lignocaine 0.2 ml | 5.77 |
| 20% Soybean emulsion 2 ml+4% lignocaine 0.4 ml | 5.77 |

that caused by injection of 1% propofol mixed with either 1% lignocaine or hydrochloric acid 0.0064 mol litre$^{-1}$ in the same ratio. The difference in pain rating between 1% propofol mixed with 1% lignocaine and 1% propofol mixed with hydrochloric acid 0.0064 mol litre$^{-1}$ was not significant (table 2).

There was a difference in pain rating between the patients' two hands even when identical mixtures were injected. The mean difference was 1.13 (SD 1.06) ($n$=15). This "subject reporting error" may be considered as a methodological error of the pain rating.

### *IN VITRO* EXPERIMENTS

The pH of the 1% Diprivan formulation varied between 7.97 and 8.02, while the pH of 1% lignocaine was 6.75. The resulting pH after mixing 1% Diprivan with 1% lignocaine in a ratio 10 to 1 was 6.32. An even lower pH was measured after increasing the volume of 1% lignocaine or increasing the lignocaine concentration (table 3). It is noticeable that the pH of this mixture was lower than that of 1% Diprivan or 1% lignocaine. A similar pH was obtained by mixing Diprivan with hydrochloric acid 0.0064 mol litre$^{-1}$ in the same ratio.

A typical pH curve is shown in figure 1.

*Table 5* Concentration (g litre$^{-1}$) and deviation (%) of propofol in the aqueous phase of a commercial preparation (1% Diprivan) *per se* and after addition of saline, 1% lignocaine or hydrochloric acid (HCl) 0.0064 mol litre$^{-1}$ in a ratio of 10+1

| Mixture | Concentration | Deviation |
|---|---|---|
| 1% Diprivan | 0.495 | |
| 1% Diprivan+saline | 0.476 | — |
| | *vs* | *vs* |
| 1% Diprivan+1% lignocaine | 0.376 | −21% |
| 1% Diprivan+HCl 0.0064 mol litre$^{-1}$ | 0.392 | −18% |

The soybean oil concentration of 1% Diprivan is 10%. Increasing volumes of 4% lignocaine added to both 10% and 20% soybean oil mixtures resulted in further lowering of the pH (table 4).

Diprivan 10 mg ml$^{-1}$ mixed with 1% lignocaine (10+1) separated into two immiscible layers within a few days, whereas 1% Diprivan mixed with saline or hydrochloric acid 0.0064 mol litre$^{-1}$, respectively, appeared stable on prolonged storage at room temperature. No macroscopic changes in these solutions were seen when stored in the dark for several months.

The concentration of propofol in the aqueous phase of 1% Diprivan was 0.495 g litre$^{-1}$. The aqueous concentration of propofol decreased in proportion when 1% Diprivan was mixed, and thus diluted, with saline. Diprivan 1% mixed with 1% lignocaine or hydrochloric acid 0.0064 mol litre$^{-1}$ (10+1) was also analysed regarding the concentration of propofol in the aqueous phase of these mixtures. The concentrations of propofol in the aqueous phase decreased markedly when either 1% lignocaine or hydrochloric acid 0.0064 mol litre$^{-1}$ was added (table 5).

The concentration of lignocaine in this phase was 1.015 g litre$^{-1}$. This concentration did not differ from that expected.

## Discussion

After addition of 1% lignocaine or hydrochloric acid 0.0064 mol litre$^{-1}$, 1% Diprivan caused less pain on injection compared with addition of saline. Addition of 1% lignocaine to 1% Diprivan caused propofol to migrate from the aqueous phase of the 1% Diprivan emulsion into its lipid phase. This migration was accompanied by a change in pH. There was an inverse relationship between pH and amount of lignocaine added, not only to 1% Diprivan but also to the soybean emulsion (Intralipid) in which propofol is formulated. An increased proportion of propofol in the lipid phase caused less pain on injection.[6,7] The lesser discomfort caused by injection of a mixture of lignocaine and propofol, compared with for example saline and propofol, may be explained only partly by the local anaesthetic action of lignocaine. This is suggested by the fact that lignocaine mixed and administered together with propofol is more effective in preventing pain on injection than pretreatment with lignocaine.[3 10] Propofol- induced pain on injection occurs quite slowly[10] giving lignocaine an opportunity to induce local anaesthesia. However, the amount of lignocaine and the injection technique are not the only important factors, but also local factors such as the contact between lignocaine and the vascular endothelium. Prolonging the effect of i.v. lignocaine on the vascular endothelium by proximal venous stasis eliminates the pain caused by subsequent injection of propofol.[12 13]

We observed a decreased incidence of pain on injection caused by 1% Diprivan when mixed with lignocaine. It is known[14] that the pH of the 1% Diprivan solution decreases when lignocaine is added and that this decrease is greater for larger doses of lignocaine. The question we tried to elucidate in this study was whether or not analgesia is obtained by local anaesthesia from lignocaine or indirectly from the decrease in pH. Therefore, a similar change in pH was created by adding hydrochloric acid to the 1% Diprivan. The results showed that the addition of hydrochloric acid to 1% Diprivan produced pain relief and that local anaesthesia by lignocaine was the less important factor for pain relief. There are three reasons for this: (1) pain prevention is instantaneous and the onset of anaesthesia from a local anaesthetic usually takes some time; (2) the concentration of lignocaine was less than 0.1%, too low for rapid onset of anaesthesia; and (3) the pH of the solution was so low that the proportion of lipophilic and diffusible free base of the lignocaine was insignificant in the water phase of the solution from which the local anaesthetic would be expected to come.

Comparisons between groups of patients are difficult to interpret as highly variable pain ratings were reported after injection of the same test solution in the same patient. This might be because of variations in the technique and rate of injection (although these were standardized as far as possible), in the area of vascular endothelium exposed to the solution and intra-individual differences in pain perception of blood vessels. This variation contributed to difficulties in isolating the effect of pH alone. Theoretically, a lower pH gives a higher fraction of propofol in an uncharged form with higher partition to the micelles of the soybean emulsion. Efforts have been made to change the emulsion formulation. Addition of blood to propofol[15] increases the amount of propofol in the emulsion phase. Also, an increased amount of fat decreases the aqueous partition of propofol by nearly 60%.[11] This deviation is more pronounced than that observed for 1% Diprivan and 1% lignocaine, and 1% Diprivan and hydrochloric acid 0.0064 mol litre$^{-1}$ (−21% and −18%, respectively) compared with 1% Diprivan and saline. However, the main difference between our findings and theirs is that we detected a higher concentration of propofol in the aqueous phase. It is reasonable to assume that this difference was caused by different methodological procedures (equilibrium dialysis[11] *vs* ultracentrifugation (this study), respectively). Also, micelles may be soluble in both the aqueous and lipid phases of the emulsion. Because of this difference, the main focus should be on the physicochemical events and changes, not absolute levels.

The pH of the solution resulting from mixing 1% Diprivan with 1% lignocaine was even lower than the pH of the two ingredients by themselves. This finding might be because of changes in the surface area structure of the micelles. The decrease in pH *per se* does not cause the emulsion to stratify, as the mixture between 1% propofol and HCl 0.0064 mol litre$^{-1}$ is macroscopically stable for several months. The same is not true when 1% lignocaine is mixed with 1% propofol.[16]

The mechanism by which propofol induces pain on injection is still not known. The release of kininogens may contribute to its origin[10 17] while vascular prostaglandin receptors do not seem to be important.[18] Local anaesthetics may bind to the vascular endothelium and binding of the local anaesthetic directly to propofol might also reduce its analgesic effects. Such an effect might explain the observed reduction of propofol-induced pain on injection by metoclopramide,[19] a structural analogue of procainamide but almost entirely lacking in local anaesthetic activity. However, a pH-lowering effect of the metoclopramide solution might also now be suggested as the principal mechanism for the reported pain relieving effect.

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# Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers†

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## Summary

We have compared the incidence of CNS symptoms and changes in echocardiography and electrophysiology during i.v. infusions of ropivacaine, bupivacaine and placebo. Acute tolerance of i.v. infusion of 10 mg $min^{-1}$ was studied in a crossover, randomized, double-blind study in 12 volunteers previously acquainted with the CNS effects of lignocaine. The maximum tolerated dose for CNS symptoms was higher after ropivacaine in nine of 12 subjects and higher after bupivacaine in three subjects. The 95% confidence limits for the difference in mean dose between ropivacaine and bupivacaine were −30 and 7 mg. The maximum tolerated unbound arterial plasma concentration was twice as high after ropivacaine ($P<0.001$). Muscular twitching occurred more frequently after bupivacaine ($P<0.05$). The time to disappearance of all symptoms was shorter after ropivacaine ($P<0.05$). A threshold for CNS toxicity was apparent at a mean free plasma concentration of approximately 0.6 mg $litre^{-1}$ for ropivacaine and 0.3 mg $litre^{-1}$ for bupivacaine. Bupivacaine increased QRS width during sinus rhythm compared with placebo ($P<0.001$) and ropivacaine ($P<0.01$). Bupivacaine reduced both left ventricular systolic and diastolic function compared with placebo ($P<0.05$ and $P<0.01$, respectively), while ropivacaine reduced only systolic function ($P<0.01$). (*Br. J. Anaesth.* 1997; **78**: 507–514).

**Key words**
Anaesthetics local, ropivacaine. Anaesthetics local, bupivacaine. Cardiovascular system, effects. Central nervous system, effects. Pharmacodynamics.

The acute and most serious adverse effects of local anaesthetics involve the cardiovascular and central nervous (CNS) systems. They are usually because of accidental intravascular or intrathecal injections, or a pronounced overdose. CNS symptoms of local anaesthetic toxicity occur before cardiovascular symptoms and signs, and include numbness of the tongue, light-headedness, visual disturbances and muscular twitching; more serious signs include convulsions, coma, respiratory arrest and cardiovascular depression. Death, probably after intravascular administration of bupivacaine and etidocaine,[1] prompted studies on the mechanism of the cardiotoxic effects of local anaesthetics and search for drugs with less cardiotoxicity.[2]

Ropivacaine is a new, long-acting local anaesthetic, related structurally to bupivacaine and mepivacaine, used as the hydrochloride of the S-enantiomer, whereas bupivacaine and mepivacaine are racemic mixtures. It is less lipid soluble than bupivacaine,[3] but its pharmacokinetic disposition is similar.[4] In preclinical studies, ropivacaine showed less CNS and cardiac toxicity than bupivacaine.[5] Studies in volunteers and patients suggest that ropivacaine is similar to bupivacaine in onset, duration and extent of sensory block, although motor block is less intense and of shorter duration.[6–9]

The objective of this study was to determine if ropivacaine is tolerated better than bupivacaine when given as an i.v. infusion to volunteers, and also to evaluate the pharmacodynamic effects in relation to arterial and venous plasma concentrations.

## Subjects and methods

We studied 12 healthy male subjects (table 1) who were assessed by physical examination, echocardiography, chest radiography and routine blood tests. No subject was receiving any medication or had a history of allergic reaction to local anaesthetics of the amide type.

The study was approved by the Ethics Committee of the Sahlgrenska University Hospital and written informed consent was obtained.

### DRUG ADMINISTRATION

Drugs were administered according to a randomized (Latin squares), double-blind, crossover design to compare ropivacaine and bupivacaine with placebo; four subjects were allocated randomly to each of the

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three treatments. Before the study, all subjects were familiarized with the initial CNS effects of i.v. lignocaine (Xylocard 100 mg 5 $ml^{-1}$, Astra Hässle AB, Mölndal, Sweden, batch RB531) at a rate of 100 mg $min^{-1}$. Ten subjects received the full 200-mg dose and two subjects 180 mg. CNS symptoms appeared in all subjects and disappeared within 5–20 min. Lignocaine infusion was given between 3 and 111 (mean 34) days before the first blind infusion.

Before each blind infusion, subjects fasted for at least 6 h. Two i.v. cannulae were inserted into antecubital veins, one in each arm, and an arterial cannula in the left radial artery. Allen's test was performed before arterial cannulation to ensure normal collateral circulation through the ulnar artery. On six occasions, subcutaneous injection of 1% lignocaine 1 ml was given 30 min to 2 h before administration of the study drug to anaesthetize the skin before insertion of the arterial cannula. Subcutaneous injection of 1% mepivacaine 1 ml was given once because of painful insertion of the catheter. A transoesophageal atrial stimulation (TAS) electrode (Medtronic 6992) was introduced, after which the subjects rested for 30 min.

Each subject received ropivacaine 5 mg $ml^{-1}$ (Astra Pain Control, Sweden, batch 471-24-1), bupivacaine 5 mg $ml^{-1}$ (Astra Pain Control, Sweden, batch 417-46-1) and placebo (sodium chloride 9 mg $ml^{-1}$; Astra Pain Control, Sweden, batch 400-62-1) by i.v. infusion (Imed 960 volumetric infusion pump, Imed Scandinavia, Sweden). Different arms were used for drug infusion and blood sampling. The infusion rate was 2 ml $min^{-1}$, corresponding to 10 mg $min^{-1}$ of active drug.

Subjects were observed continuously by the attendant anaesthetist and were asked frequently open questions to describe any symptoms during and after infusion until complete disappearance of all symptoms. The infusion was discontinued at definite signs and symptoms of CNS effects or at the request of the subject. Otherwise, a maximum dose of 250 mg was given. In practice, no infusion was discontinued at the request of the subject. The subjects were recumbent during and for up to 2 h after infusion. The mean number of days between blind infusions was 50 (range 3–179).

### ASSESSMENT OF CARDIOVASCULAR EFFECTS

A 12-lead ECG was recorded every 2–3 min from 5 min before and until 5 min after the infusion was stopped, and then 10 min after the end and 2 h after the start of the infusion. PQ interval, QRS width and QT intervals from the Q wave to the end of the T wave, QTe, and to the top of the T wave, QTt, were recorded and QTc calculated. The electrocardiographic variables were measured as the mean of five consecutive values. The same variables were recorded during TAS, 5 min before and immediately after the infusion had been stopped and the echocardiogram had been recorded. Stimulation was applied at 100 or 120 beat $min^{-1}$, or both, in order to achieve comparable heart rates.

Doppler echocardiography was performed using an Acuson 128 XP computed sonograph equipped with a 2.5-MHz transducer. All subjects were investigated in a slightly left lateral supine position. Echocardiograms were obtained 5 min before starting the infusion and then repeatedly every 3 min until the end of infusion. Echocardiograms after infusion were recorded 5 and 10 min after the end of infusion and 2 h after the start. Standard parasternal and apical views were stored on videotape. Cross-sectional M-mode recordings were made on chart paper at a speed of 50 mm $s^{-1}$ for off-line measurements of left ventricular (LV) end-diastolic and end-systolic dimensions. Ejection fraction (EF), stroke volume and cardiac output were calculated according to the formulae of Teichholz and colleagues.[10] Colour Doppler was used for detection of valvular regurgitation at the mitral, aortic and tricuspid valves before and after infusion. Any regurgitation was denoted on a scale from 1 to 4, where 1 was small haemodynamically insignificant flow and 4, large acute regurgitation. Evaluation of regurgitant flows was made off-line by the echocardiographer blinded to the subjects. Pulsed-wave Doppler was used to record transmitral flow velocities from the apical four-chamber view, with the sample volume placed at the tips of the mitral leaflets. Doppler recordings were made on chart paper at a speed of 100 mm $s^{-1}$. The ratio of maximal flow velocities at atrial contraction (A) and early filling wave (E) was calculated as a variable of LV diastolic function. Transmitral flow deceleration time (MV dec), reflecting early diastolic properties of the left ventricle, was also measured. All echocardiographic and Doppler values represent the average of three consecutive cardiac cycles.

Intra-arterial systolic and diastolic arterial pressures were recorded before starting the infusion and every 1 min until the end, and also every 5 min until 30 min after the end of infusion.

Subjects were monitored for 4 h after infusion. A follow-up comprising physical examination and clinical laboratory tests was performed 2–3 weeks later.

### BLOOD SAMPLING AND DRUG ASSAY

Samples of 5 ml of arterial and venous blood were obtained (Venoject) immediately before drug administration, and 2, 5, 10, 15, 20, 25, 30, 35 and 45 min, and 1 and 2 h after starting the infusions.

Plasma was separated within 1 h of collection, frozen immediately and stored at −20 °C. Total concentrations of ropivacaine and bupivacaine base were measured by gas chromatography.[11] The limit of quantification of the method was 0.008 mg $litre^{-1}$, interassay precision approximately 5% and recovery close to 100%. Free concentrations of ropivacaine and bupivacaine were assayed by coupled-column liquid chromatography after ultrafiltration of the plasma samples. Ropivacaine and bupivacaine were detected by UV at 210 nm and the limit of measurement was 0.003–0.008 mg $litre^{-1}$.[12] Intra-assay precision was 3–9 % for the two drugs determined from spiked plasma samples.

### STATISTICAL METHODS

A sample size of 12 subjects was determined to have a power of approximately 90% and a type I error of 5% based on a mean difference in tolerated i.v. dose of 26 mg and with an SD of 25 mg.[13]

The main analyses of treatment differences were based on a parametric model assuming Gaussian distributed errors. A general linear (ANOVA) model comprising effects for subject, period, direct treatment and (residual) error was used to describe the variation in dependent variables. Tests for equality between all three treatments were performed using $F$ tests and pairwise treatment comparisons with the two-sided $t$ test using $\alpha \leq 0.05$ in all tests. Data from all three treatment groups were used to estimate residual (error) variance. In addition to the tests, 95% confidence intervals for pairwise treatment differences were calculated.

Concentration data were collected only for bupivacaine and ropivacaine treatment periods.

The association between dose or drug concentration and physiological effects and tolerance was evaluated. Symptoms were grouped in different categories before breaking the code. Total and unbound drug plasma concentrations were estimated in arterial and venous blood. The probability of experiencing CNS symptoms with increasing concentrations was estimated in plots of arterial free plasma concentration at the start of symptoms compared with the cumulative number of subjects with symptoms. The actual plasma concentration at the onset of symptoms was interpolated linearly between two adjacent points if no value was available at the time of measurement. The analysis was based on symptoms grouped in the following categories: hearing and/or visual disturbances, perioral numbness, tingling, paraesthesia and/or paralysis, muscular twitching and/or muscular rigidity, and dysarthria. The accumulated frequencies of various symptoms were classified into categories.

Data are reported as mean (SD).

## Results

### MAXIMUM TOLERATED DOSES

Nine of 12 subjects tolerated a higher and three a lower dose of ropivacaine compared with bupivacaine. All subjects tolerated the full placebo dose (table 1). The mean dose of ropivacaine (115 mg) was higher than that of bupivacaine (103 mg) (ns). The estimated 95% confidence limits for the difference in means between ropivacaine and bupivacaine were −30 and 7 mg.

### MAXIMUM TOLERATED PLASMA CONCENTRATIONS

Unbound arterial plasma concentrations at the end of infusion, that is at the maximum tolerated dose, were consistently higher in all subjects after ropivacaine (table 1), and individual concentration ratios of ropivacaine to bupivacaine ranged from 1.2 to 4.7. Mean arterial unbound plasma concentrations were approximately twice as high after ropivacaine than after bupivacaine ($P<0.001$). Total and unbound venous and total arterial plasma concentrations were similar after both drugs (table 2). Total and unbound arterial plasma concentrations were consistently higher than corresponding venous concentrations with both drugs during and up to 20 min after the end of infusion.

### CNS SYMPTOMS

Symptoms of CNS toxicity occurred in all subjects during administration of active drug. The first symptom appeared after 2–8 min of infusion of both drugs. The most common symptoms were visual and hearing disturbances, dysarthria, tingling, perioral numbness, dizziness, paraesthesia, light-headedness, muscular twitching and muscular rigidity (fig. 1). More subjects reported muscular twitching after bupivacaine ($P<0.05$). After placebo, one subject

*Table 1* Subject characteristics, maximum tolerated doses and free arterial plasma concentrations of ropivacaine (Rop.) and bupivacaine (Bup.) at the end of i.v. infusion of 10 mg $min^{-1}$. Crossover study in 12 volunteers. *Sodium chloride 9 mg $ml^{-1}$

| | | | | Dose | | | Unbound arterial concn | |
|---|---|---|---|---|---|---|---|---|
| Subject No. | Age (yr) | Weight (kg) | Height (cm) | Rop. (mg) | Bup. (mg) | Placebo (ml)* | Rop. (mg $litre^{-1}$) | Bup. (mg $litre^{-1}$) |
| 1 | 23 | 83 | 194 | 90 | 70 | 50 | 0.57 | 0.26 |
| 2 | 28 | 85 | 191 | 90 | 125 | 50 | 0.62 | 0.42 |
| 3 | 33 | 91 | 182 | 120 | 90 | 50 | 0.34 | 0.13 |
| 4 | 29 | 85 | 185 | 110 | 95 | 50 | 0.57 | 0.35 |
| 5 | 27 | 90 | 184 | 130 | 165 | 50 | 0.59 | 0.51 |
| 6 | 29 | 82 | 186 | 160 | 120 | 50 | 0.50 | 0.30 |
| 7 | 29 | 75 | 177 | 150 | 135 | 50 | 0.62 | 0.44 |
| 8 | 28 | 82 | 184 | 85 | 70 | 50 | 0.49 | 0.24 |
| 9 | 29 | 81 | 183 | 150 | 85 | 50 | 0.69 | 0.34 |
| 10 | 28 | 90 | 190 | 70 | 100 | 50 | 0.41 | 0.21 |
| 11 | 27 | 81 | 187 | 120 | 100 | 50 | 0.42 | 0.28 |
| 12 | 28 | 74 | 176 | 105 | 85 | 50 | 0.85 | 0.18 |
| Mean | 28 | 83 | 185 | 115 | 103 | 50 | 0.56 | 0.30 |
| SD | 2.2 | 5.4 | 5.3 | 29 | 30 | | 0.14 | 0.11 |
| Min. | 23 | 74 | 176 | 85 | 70 | | 0.34 | 0.13 |
| Max. | 33 | 91 | 194 | 160 | 165 | | 0.85 | 0.51 |

*Table 2* Maximum tolerated plasma concentrations of ropivacaine and bupivacaine at the end of i.v. infusion of 10 mg $\text{min}^{-1}$ (mean SD) (min.–max.) Crossover study in 12 volunteers. *** $P<0.001$ (ropivacaine *vs* bupivacaine)

| | Plasma concentration (mg $\text{litre}^{-1}$) | |
|---|---|---|
| Sampling/drug | Total | Unbound |
| Arterial | | |
| Ropivacaine | 4.3 (0.6) | 0.56 (0.14)*** |
| | (3.4–5.3) | (0.34–0.85) |
| Bupivacaine | 4.0 (1.4) | 0.30 (0.11) |
| | (1.1–6.2) | (0.13–0.51) |
| Venous | | |
| Ropivacaine | 2.2 (0.8) | 0.15 (0.08) |
| | (0.5–3.2) | (0.01–0.24) |
| Bupivacaine | 2.1 (1.2) | 0.11 (0.10) |
| | (0.8–4.5) | (0.01–0.38) |

reported tremor in the chin and another paraesthesia in the arms and numbness in the thumb, but the infusion was not interrupted.

Objective signs, for example muscular rigidity, muscular twitching and dysarthria, were frequent end-points for stopping the infusion, and one or more of these signs or other symptoms were observed in 10 subjects after ropivacaine and in all subjects after bupivacaine. The time from the end of infusion to disappearance of all symptoms was shorter after ropivacaine (13 (11) min) than after bupivacaine (20 (16) min) ($P<0.05$).

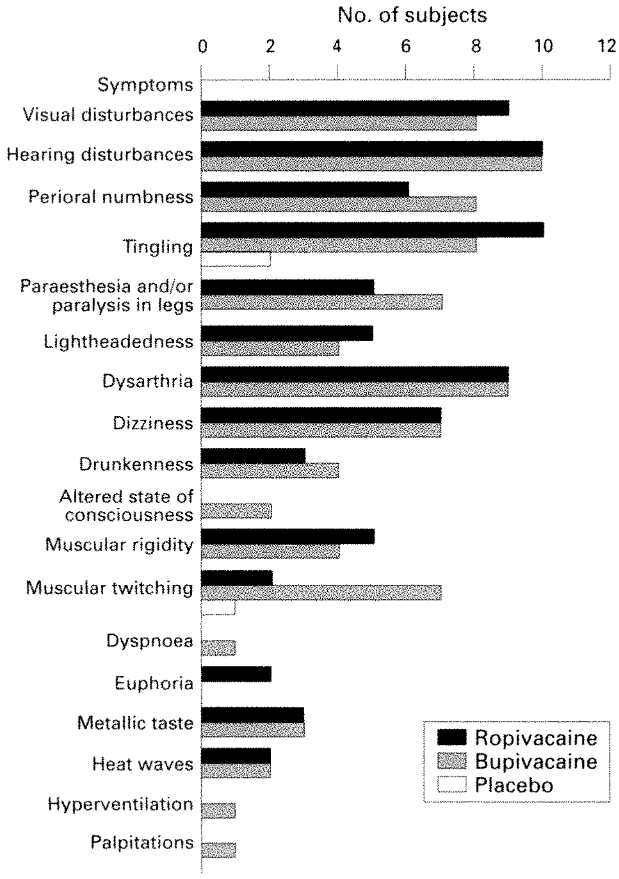

*Figure 1* Number of subjects with symptoms, grouped in different categories, during and after i.v. infusion of ropivacaine and bupivacaine 10 mg $\text{min}^{-1}$ and placebo (saline). Crossover study in 12 volunteers.

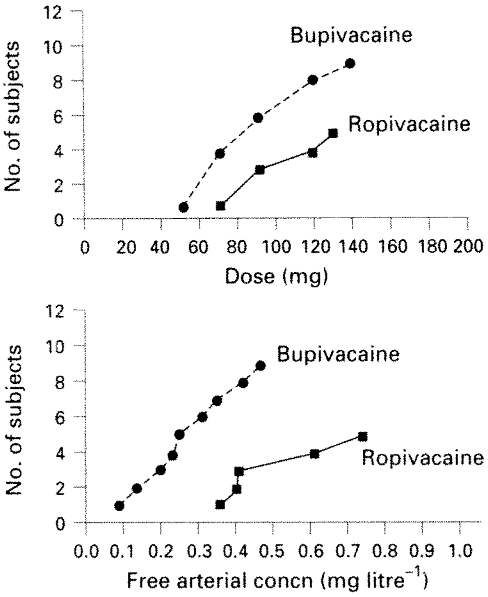

*Figure 2* Cumulative number of subjects with muscular twitching or rigidity, or both, against dose (top) or unbound arterial plasma concentration (bottom) at onset of i.v. infusion of ropivacaine and bupivacaine 10 mg $\text{min}^{-1}$. Crossover study in 12 volunteers.

Ropivacaine dose–response and concentration–response curves for CNS symptoms were shifted consistently to the right compared with those of bupivacaine. This shift meant that symptoms of CNS toxicity appeared earlier and in more subjects at a certain dose or plasma concentration when bupivacaine was given. This difference between drugs was more pronounced for muscular twitching and muscular rigidity (fig. 2) than for dysarthria.

### ARTERIAL PRESSURE AND HEART RATE

Both drugs increased systolic arterial pressure compared with placebo (table 3) ($P<0.001$). The mean increase in systolic pressure was 7% after ropivacaine and 9% after bupivacaine.

Bupivacaine was associated with an increase in diastolic arterial pressure in all subjects ($P<0.001$ *vs* placebo), whereas diastolic pressure increased in 10 of 12 subjects given ropivacaine. The mean increase was larger (26%) after bupivacaine than that after ropivacaine (13%) ($P<0.05$ *vs* placebo). There was a 12% increase in heart rate after both ropivacaine and bupivacaine ($P<0.01$ and $P<0.001$ *vs* placebo).

### ELECTROCARDIOGRAPHY

Bupivacaine increased QRS width in nine of 12 subjects at the end of infusion (fig. 3). The increase (6%) was significant relative to that for ropivacaine (three of 9 subjects (2.4%)) ($P<0.05$) and placebo (−0.4%) ($P<0.05$). During TAS at 120 beat $\text{min}^{-1}$, both ropivacaine (8.5%) and bupivacaine (9%) showed a significant increase in QRS width compared with placebo ($P<0.05$). PQ interval and QTc did not change.

QTt decreased in eight of nine subjects given ropivacaine and in 10 of 12 subjects given bupivacaine, with mean decreases of −5.7% and −5.3%. QTe decreased in all nine subjects given ropivacaine and

*Table 3* Haemodynamic, echocardiographic and electrocardiographic changes (mean (SD))at maximum tolerated doses after i.v. infusion of ropivacaine and bupivacaine 10 mg $min^{-1}$ and placebo (saline). Crossover study in 12 volunteers. *Heart rate was measured from the ECG on the M-mode recordings. Statistically significant differences are given in the text

| | Ropivacaine | | Bupivacaine | | Placebo | |
|---|---|---|---|---|---|---|
| Variable | Baseline | End of infusion | Baseline | End of infusion | Baseline | End of infusion |
| | (*n*=12) | (*n*=12) | (*n*=12) | (*n*=12) | (*n*=12) | (*n*=12) |
| HR (beat $min^{-1}$) | 60 (9) | 68 (7) | 60 (10) | 68 (10) | 62 (15) | 58 (10) |
| SAP (mm Hg) | 143 (13) | 152 (16) | 141 (14) | 154 (17) | 138 (14) | 134 (11) |
| DAP (mm Hg) | 72 (8) | 81 (10) | 69 (5) | 87 (12) | 66 (8) | 68 (7) |
| Echocardiography) | (*n*=12) | (*n*=12) | (*n*=12) | (*n*=12) | (*n*=12) | (*n*=12) |
| $LVID_d$ (cm) | 5.4 (0.2) | 5.5 (0.5) | 5.4 (0.3) | 5.4 (0.3) | 5.4 (0.3) | 5.4 (0.3) |
| $LVID_S$ (cm) | 3.7 (0.3) | 4.0 (0.4) | 3.6 (0.3) | 4.0 (0.3) | 3.8 (0.3) | 3.7 (0.3) |
| EF (%) | 59 (6) | 52 (8) | 60 (7) | 52 (6) | 56 (7) | 59 (5) |
| MV dec (ms) | 166 (13) | 157 (20) | 165 (34) | 152 (27) | 168 (21) | 176 (27) |
| A/E) | 0.60 (0.12) | 0.64 (0.13) | 0.60 (0.14) | 0.66 (0.13) | 0.54 (0.13) | 0.56 (0.13) |
| SV (ml) | 85 (11) | 78 (21) | 84 (16) | 74 (14) | 77 (11) | 83 (10) |
| CO (litre $min^{-1}$) | 5.4 (1.1) | 5.3 (1.6) | 5.2 (1.2) | 5.4 (1.7) | 4.8 (1.3) | 4.8 (0.7) |
| HR (beat $min^{-1}$)* | 64 (8) | 67 (9) | 63 (12) | 73 (16) | 62 (13) | 59 (9) |
| Electrocardiography) | (*n*=9) | (*n*=10) | (*n*=12) | (*n*=12) | (*n*=12) | (*n*=12) |
| QRS (ms) | 94 (7) | 98 (7) | 94 (6) | 99 (8) | 94 (7) | 93 (7) |
| PQ (ms) | 169 (23) | 180 (21) | 171 (13) | 179 (18) | 173 (17) | 175 (21) |
| QTc (ms) | 397 (23) | 408 (28) | 394 (20) | 406 (19) | 397 (25) | 397 (22) |
| QTe (ms) | 404 (23) | 392 (21) | 400 (26) | 390 (22) | 401 (24) | 403 (24) |
| QTt (ms) | 303 (16) | 287 (18) | 299 (19) | 283 (21) | 298 (20) | 305 (20) |
| QTe–QTt (ms) | 101 (13) | 105 (15) | 101 (13) | 107 (19) | 103 (7) | 99 (10) |

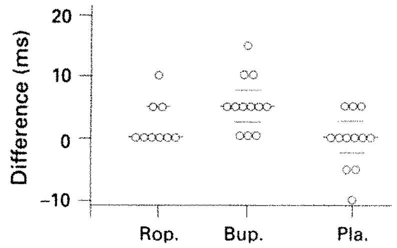

*Figure 3* Individual (median, 25% and 75 % quartiles) differences in QRS width during sinus rhythm between the value at the end of infusion and baseline and at the maximum tolerated dose after i.v. infusion of ropivacaine (Rop.) and bupivacaine (Bup.) 10 mg $min^{-1}$ and placebo (Pla.) (saline). Crossover study in 12 volunteers.

in nine of 12 subjects after bupivacaine. Mean decreases were −3.3% and −2.5%.

On assessing the last portion of the T-wave, the (QTe-QTt) was found to have increased in four of nine subjects after ropivacaine, four of 12 subjects after bupivacaine, and in one of 12 subjects after placebo, with mean increases of 3.8% and 5.8% and a mean decrease of −3.7%, respectively. Cardiac arrhythmias were not detected.

## ECHOCARDIOGRAPHY

### *Diastolic function*

There was a shorter transmitral flow deceleration time in six of 12 subjects when bupivacaine was administered (−8.1%, $P<0.05$ *vs* placebo) compared with −5.5% after ropivacaine (fig. 4). The A/E ratio increased by a mean of 6.2% for ropivacaine and 9.3% for bupivacaine (ns).

### *Systolic function*

Left ventricular ejection fraction decreased in nine of 12 subjects after ropivacaine and in 11 of 12 subjects after bupivacaine. The mean changes in ejection fraction were −11.6% compared with −13.8% ($P<0.01$ *vs* placebo for both drugs) (fig. 4). Stroke volume decreased an average of −8.1% after ropivacaine and −12.1% after bupivacaine ($P<0.05$ *vs* placebo).

Cardiac output decreased in eight of 12 subjects given ropivacaine (−2.5%) and in five of 12 subjects given bupivacaine (−3.7%). One subject had a large

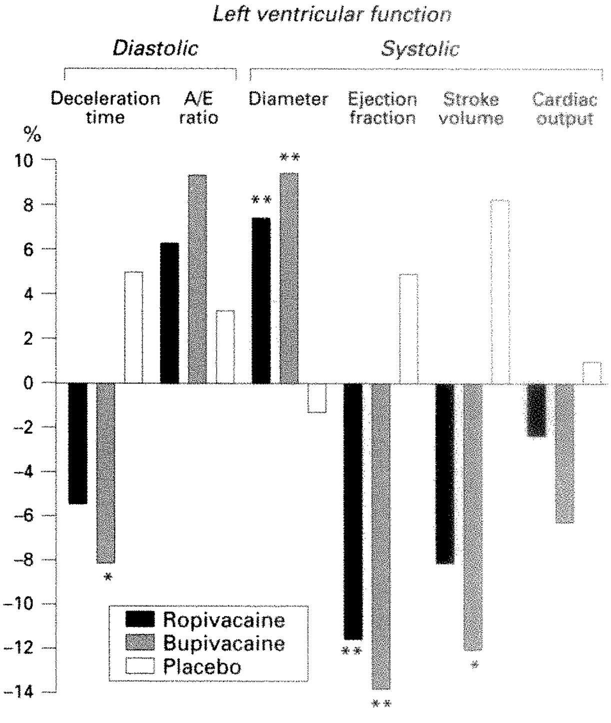

*Figure 4* Mean percentage differences in echocardiographic variables between the value at the end of infusion and baseline and at the maximum tolerated dose after i.v. infusion of ropivacaine and bupivacaine 10 mg $min^{-1}$ and placebo (saline). Crossover study in 12 volunteers.

increase in cardiac output, however, when given bupivacaine (169%), in relation to a transient increase in heart rate from 51 to 110 beat $min^{-1}$. When this subject was excluded from analysis, the mean change in the bupivacaine group was −6.4%.

No subject showed signs of pathological valvular regurgitation according to colour Doppler findings before or after infusion.

### ADVERSE EFFECTS

Transient pain and tenderness at the arterial cannulation site were reported by one subject during one blind infusion. No other adverse events occurred.

## Discussion

Tolerance of local anaesthetics has been assessed in volunteers given continuous i.v. infusions.[13–18] In general, the threshold decreases with increase in the infusion rate[16] because the maximum plasma concentration is directly proportional to the dose and inversely proportional to cardiac output and infusion time.[18] In our study, the infusion rate of 10 mg $min^{-1}$ was a rational compromise between the maximum dose allowed and the time within which the short-lasting effects could be recorded.

In all subjects receiving an active drug, the infusion was stopped because of CNS symptoms before any arrhythmia or other clinically significant changes in haemodynamic state or electrocardiography occurred. However, the results showed statistically significant changes in both cardiac conduction and contractility. These data, supported by preclinical studies showing that ropivacaine is less CNS and cardiotoxic than bupivacaine,[5] suggest that the potential of ropivacaine to produce CNS and cardiotoxicity is also less in humans. The general pattern of increasing CNS symptoms and signs and their order was similar to that reported previously with other local anaesthetics.[18]

Ropivacaine and bupivacaine produced a similar spectrum of symptoms involving the CNS, but the duration of symptoms was shorter after ropivacaine. Occasionally, early CNS symptoms made subjects temporarily unable to communicate their sensations reliably. Signs of excitatory CNS effects such as dysarthria, shivering, muscular twitching and muscular rigidity were frequent end-points for drug administration. Thus although the decision when to discontinue the infusion of necessity contains a subjective element, the decision to stop the infusion in this study could in all but two cases be based on objective criteria that were observed easily by the attending physician. This was probably made feasible by allowing higher maximum doses in this compared with the previous study[13] where the infusion was stopped after 150 mg regardless of symptoms. In our study nine of the 12 subjects tolerated a higher dose of ropivacaine than bupivacaine, which is comparable with corresponding results in 10 of 12 subjects in the study of Scott and colleagues.[13] The sequences of drug administration as a result of randomization in the three subjects who tolerated a higher dose of bupivacaine did not differ from sequences in subjects who tolerated a higher dose of ropivacaine. Moreover, all subjects tolerated higher unbound plasma concentrations of ropivacaine than bupivacaine, which also renders unlikely any effect caused by the sequence of drug administration.

Differences between ropivacaine and bupivacaine were identified in terms of tolerated doses, maximum tolerated free plasma concentrations and time to disappearance of symptoms. The consistent shift to the right of the ropivacaine dose–response and concentration–response curves for CNS symptoms implied that higher doses and free plasma concentrations of ropivacaine were tolerated before symptoms were elicited.

Arterial blood carries local anaesthetic to various parts of the body after systemic administration, while peripheral venous blood returning from poorly perfused sampling tissues during rapid i.v. administration is not representative of the distribution to, and concentration at, the site of action for central effects of local anaesthetics.[19 20] This is in agreement with the large arteriovenous concentration differences seen in our study. It is the free or unbound drug that is available for distribution, crossing biological membranes and binding to receptor sites where pharmacological effects are initiated. The toxic concentration, as estimated from peripheral venous free plasma concentrations after slower systemic drug input (without a marked arteriovenous concentration difference), would therefore be similar to free arterial plasma concentrations of ropivacaine and bupivacaine related to CNS symptoms in this study with a rapid drug input. A threshold for CNS toxicity was apparent at mean free arterial plasma concentrations of the order of 0.6 mg $litre^{-1}$ for ropivacaine and 0.3 mg $litre^{-1}$ for bupivacaine. A similar threshold for free venous plasma concentration has been reported to be 0.24 mg $litre^{-1}$ after a slower continuous perineural infusion of bupivacaine.[21] In a previous study,[13] CNS and cardiovascular symptoms were associated with higher peripheral venous plasma concentrations of ropivacaine than bupivacaine although, as indicated by the authors, the use of arterial samples would have been more informative.

Cardiovascular effects were more pronounced after bupivacaine than after ropivacaine at maximum tolerated doses. Although there were statistically significant changes, they were generally small and unremarkable. A similar distinction between ropivacaine and bupivacaine in the dose–response in QRS width has been reported in anaesthetized pigs.[22] The difference in systemic toxicity between ropivacaine and bupivacaine is likely to be clinically important.

In general, the cardiovascular system is more resistant to the effects of local anaesthetics than the CNS.[23] Extremely high concentrations depress spontaneous pacemaker activity in the sinus node and result in sinus bradycardia and sinus arrest. Similar depression at the AV node results in prolonged PQ/PR intervals and partial or complete AV dissociation. Local anaesthetics such as ropivacaine and bupivacaine inhibit rapid inward flow of sodium ions into cardiac cells during depolarization, thereby slowing the rate of rise of the action potential during phase 0.[24–26] Recovery from sodium channel block is faster after treatment with ropivacaine than after bupivacaine,[27] which is probably an important factor in the increased cardiotoxicity of bupivacaine. Impaired depolarization decreases cardiac contractility and increases QRS width. An increase in QRS width has been correlated with cardiotoxicity of local anaesthetics,[23] and also with quinidine and tricyclic antidepressant agents.

In this study, there was an increase in QRS width that was significantly smaller after ropivacaine than after bupivacaine; this is similar to previous findings.[13] However, our study is unique by inclusion of a placebo group, and the effect on QRS was similar after ropivacaine and placebo. The development of CNS symptoms prompted discontinuation of the infusion, which prevented an unwanted further increase in QRS width. Both QTt and the QTe intervals decreased, but not to the same degree, so that the index (QTe-QTt) increased. This change, representing a shortening of the final portion of the depolarization time, is in accord with a class IB (lignocaine-like) antiarrhythmic mode of action.

When bupivacaine was administered, both systolic and diastolic LV functions were reduced significantly compared with placebo. When using ropivacaine, only significant changes in systolic variables were noted. Ropivacaine also tended to have a shorter restoration period, although this was not tested. The significant reduction in LV ejection fraction compared with placebo was caused by an increase in LV *systolic* diameter, which might imply reduced myocardial contractility. In young individuals with borderline hypertension, it has been shown that such a small increase in systolic arterial pressure is associated with supranormal LV systolic function.[28] The increase in afterload during infusion of both drugs would not be an explanation of the observed changes in LV systolic function in this group of young, healthy individuals.

In the placebo period after the total 25 min of the investigation, there was an increase in systolic function variables, ejection fraction and stroke volume, but a decrease in heart rate with maintained cardiac output. These findings represent the normal haemodynamic reaction to the resting situation, with fluid resorption into the circulation, which increases blood volume, and increased vagal tone causing a minor decrease in heart rate.

Using echocardiography, Scott and colleagues[13] reported reduced LV systolic function after i.v. administration of ropivacaine and bupivacaine. Both drugs depressed cardiac contractility after intracoronary artery injection in anaesthetized pigs.[22]

We also evaluated diastolic function. Changes in diastolic variables are influenced by several factors, such as heart rate, sympathetic tone and loading conditions. The techniques available for measuring diastolic function are limited in different ways. Using pulsed wave Doppler, we noted a difference between ropivacaine and bupivacaine in LV filling pattern compared with placebo. Our findings indicated changes towards a more restrictive filling pattern and reduced LV compliance with bupivacaine.

There were remarkably few placebo effects on the CNS and cardiovascular system.

Ropivacaine showed a higher tolerated dose and unbound plasma concentration based on the shift in dose–response and concentration–response curves for CNS symptoms. At doses producing CNS symptoms, cardiovascular changes, such as depression of conduction and diastolic function, were less pronounced with ropivacaine compared with bupivacaine.

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# Assessment of cardiovascular changes during laparoscopic hernia repair using oesophageal Doppler

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**Summary**

We have used an oesophageal Doppler to measure aortic blood flow velocity before, during and after induction of carbon dioxide pneumoperitoneum in 10 consecutive patients, mean age 58 yr, undergoing laparoscopic hernia repair. Derived values for stroke distance, minute distance and systemic vascular resistance showed considerable interpatient variation indicating unpredictable haemodynamic responses. Five minutes after insufflation of the abdomen there was a significant increase in mean arterial pressure from 82.5 to 103.6 mm Hg ($P<0.05$) but both stroke distance and minute distance decreased significantly (mean 12.0 (SEM 1.4) cm to 9.0 (0.7) cm, $P<0.05$; and 747.5 (82) cm min$^{-1}$ to 596 (49) cm min$^{-1}$, $P<0.05$; respectively) indicating a significant decrease in cardiac output. There was a corresponding increase in the index of systemic vascular resistance from 1092 (747) to 2079 (400) ($P<0.05$) which persisted after deflation of the abdomen. Oesophageal Doppler can provide continuous online haemodynamic data with a rapid response to acute changes and may have a role in non-invasive haemodynamic monitoring during laparoscopic procedures in older patients with cardiovascular disease. (*Br. J. Anaesth.* 1997; **78**: 515–519).

**Key words**

Surgery, laparoscopy. Cardiovascular system, effects. Measurement techniques, oesophageal Doppler.

Minimally invasive laparoscopic surgery can reduce analgesic requirements and permit earlier postoperative mobilization than equivalent open procedures.[1] It has been advocated for high-risk patients with cardiac and pulmonary disease.[2] But carbon dioxide pneumoperitoneum and the Trendelenburg position produce major haemodynamic and respiratory changes.[3 4] Studies during laparoscopic cholecystectomy have shown large variations in the magnitude of changes in cardiac output, systemic vascular resistance and mean arterial pressure.[5 6]

Laparoscopic hernia repair is a recent addition to minimally invasive surgery. Many patients undergoing this type of surgery are older men with a high incidence of cardiac and respiratory impairment. Although studies in healthy gynaecological patients have shown only minor haemodynamic changes during laparoscopic procedures, this may not apply to laparoscopic hernia repair in older patients for whom little data are available. It has been suggested that invasive haemodynamic monitoring be used in patients with pre-existing cardiovascular disease undergoing laparoscopic surgery.[7]

The aim of this study was to measure haemodynamic changes during laparoscopic hernia repair using the non-invasive technique of oesophageal Doppler. Aortic blood flow velocity and the derived haemodynamic indices of stroke distance, minute distance and systemic vascular resistance were recorded before, during and after induction of pneumoperitoneum.

## Patients and methods

After obtaining Ethics Committee approval and informed consent, we studied 10 consecutive patients, ASA I–III, undergoing elective laparoscopic inguinal hernia repair under general anaesthesia. Temazepam 20 mg orally was given as premedication 2 h before operation.

On arrival in the anaesthetic room heart rate and non-invasive arterial pressure (Dinamap) were recorded. Anaesthesia was induced using alfentanil 25 μg kg$^{-1}$, thiopentone sufficient to obtund the eyelash reflex (2–4 mg kg$^{-1}$) and atracurium 0.5 mg kg$^{-1}$, and the patient's trachea was intubated. Infusions of alfentanil 25 μg kg$^{-1}$ h$^{-1}$ and atracurium 0.5 mg kg$^{-1}$ h$^{-1}$ were commenced. The lungs were ventilated with 70% nitrous oxide in oxygen. Ventilation was initially set at a tidal volume of 10–12 ml kg$^{-1}$ with ventilatory frequency adjusted to maintain an end-tidal carbon dioxide partial pressure of 5.0–5.5 kPa. Anaesthesia was maintained with isoflurane. The end-tidal concentration (Datex Capnomac Ultima, Datex, Helsinki, Sweden) was maintained constant at 0.8–1.0 MAC in each patient until the last set of study variables had been recorded. All patients received 1 litre of Hartmann's

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solution in the perioperative period. At the end of the procedure neuromuscular block was antagonized with neostigmine and glycopyrronium. Postoperative analgesia was left to the discretion of the individual anaesthetist.

The same surgeon performed all operations in a standardized manner. Pneumoperitoneum was established by introduction of a Verres' needle via a 1.2-cm infra-umbilical incision. Two further ports were introduced laterally to facilitate surgery. The peritoneum was divided over the inguinal defect which was repaired with a mesh secured by staples. At the end of the procedure the pneumoperitoneum was released before removal of the ports and closure of the wounds.

Individual patient and procedure details are shown in table 1. Patient numbers referred to in the text correspond to the numbers given in table 1. Eight patients underwent unilateral hernia repair and two patients (Nos 2 and 8) underwent bilateral hernia repairs. Mean intra-abdominal pressure was maintained at less than 13 mm Hg at all times.

### CARDIOVASCULAR RECORDINGS

After tracheal intubation, an oesophageal Doppler probe (ODM 2, Deltex, Chichester, UK) was inserted through the patient's mouth and positioned approximately 35–40 cm from the teeth where well defined aortic blood flow signals could be detected. The probe was manipulated until the best signal was obtained. Five (M5) and 10 (M10) min after induction of anaesthesia, but before the first surgical stimulus, a set of baseline physiological variables were recorded: heart rate, arterial pressure, $Sp_{O_2}$, peak airway pressure, $FI_{O_2}$, ventilatory frequency, Doppler stroke distance and minute distance. These measurements were then repeated at the times shown in table 2.

On the oesophageal Doppler display, stroke distance is represented by the area under the flow velocity waveform and this represents the length a column of blood flows along the aorta with each ventricular systole. This is a linear index of left ventricular stroke volume. Minute distance is the product of stroke distance and heart rate and is a linear index of cardiac output. An index of systemic vascular resistance (SVRI) can be obtained by dividing mean arterial pressure by minute distance.[8]

*Table 2* Times for data collection during laparoscopic hernia repair

| Times | Description |
|---|---|
| M5 | 5 min after induction (baseline) |
| M10 | 10 min after induction |
| I+1 | 1 min after abdominal insufflation |
| I+3 | 3 min after abdominal insufflation |
| I+5 | 5 min after abdominal insufflation |
| T | Immediately after Trendelenburg positioning |
| T+5 | 5 min after Trendelenburg positioning |
| T+30 | 30 min after Trendelenburg positioning |
| EDSX | End of surgery |
| PDEF | After abdominal deflation |

Data were analysed using the Statview SE+ Graphics (Concepts Inc. Berkeley, CA, USA) statistical system. Statistical analysis was performed with a two-way analysis of variance for repeated measures and $P<0.05$ was considered significant. Results are expressed as mean (SEM).

## Results

Five minutes after insufflation of the abdomen (I+5) there was a statistically significant increase in mean arterial pressure (MAP) from 82.5 to 103.6 mm Hg ($P<0.05$) (fig. 1). Mean stroke distance (fig. 2) and minute distance decreased significantly at this time from 12.0 (1.4) to 9.0 (0.7) cm ($P<0.05$) and from 747.5 (82) to 596 (49) cm min$^{-1}$ ($P<0.05$), respectively, indicating a significant decrease in cardiac output. There was a corresponding increase in the index of systemic vascular resistance from 1092 (747) to 2079 (400) ($P<0.05$) (fig. 3).

Percentage changes from baseline (M5) in measured stroke distance and estimated SVRI are also shown for individual patients (figs 4, 5) and illustrate inter-patient variability. Pre-existing cardiovascular disease was present in patient Nos 1, 3, 8 and 9 (table 1).

Peak airway pressure increased significantly from 19.4 (1.2) to 25.7 (2.0) cm $H_2O$ ($P<0.05$) as did end-tidal carbon dioxide partial pressure from 4.3 (0.13) to 5.0 (0.1) kPa ($P<0.05$) (table 3). Mean arterial pressure remained significantly increased ($P<0.05$) throughout the procedure (fig. 1) as did end-tidal carbon dioxide partial pressure ($P<0.05$)

*Table 1* Patient characteristics and duration of surgery

| Patient No. | Sex | Age (yr) | Weight (Kg) | Previous history | Medication | ASA grade | Duration of anaesthesia (min) |
|---|---|---|---|---|---|---|---|
| 1 | F | 82 | 54 | Ischaemic heart disease, myocardial infarction | Atenolol | III | 55 |
| 2 | M | 74 | 70 | Prostatic carcinoma | Goserelin | II | 100 |
| 3 | M | 63 | 65 | Myocardial infarction, coronary artery bypass grafting | Simvastatin | III | 70 |
| 4 | M | 41 | 100 | — | | I | 70 |
| 5 | M | 54 | 65 | — | — | I | 65 |
| 6 | M | 54 | 83 | — | — | I | 60 |
| 7 | M | 70 | 77 | — | — | I | 80 |
| 8* | M | 67 | 64 | Hypertension | Frusemide,<br>amlodipine | II | 100 |
| 9 | M | 45 | 83 | Atrial fibrillation | Digoxin | II | 70 |
| 10 | M | 30 | 68 | Asthma | Salbutamol | II | 50 |
| Mean | — | 58.0 | 72.9 | — | — | — | 65.0 |

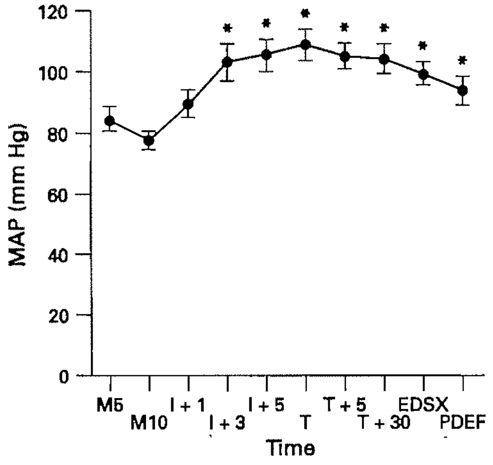

*Figure 1* Mean arterial pressure (MAP) (mean, SEM; $n=10$) during laparoscopic hernia repair. Times are those shown in table 2. *$P<0.05$.

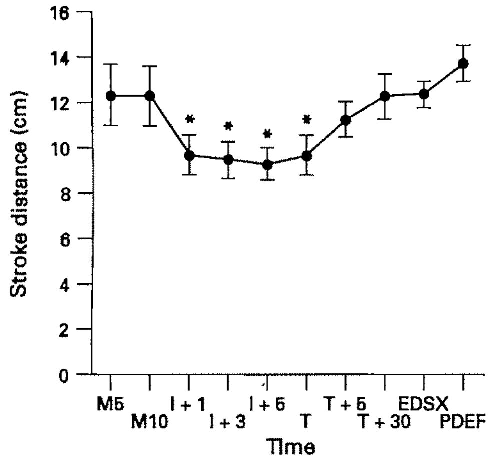

*Figure 2* Oesophageal Doppler stroke distance (mean, SEM; $n=10$) during laparoscopic hernia repair. Times are those shown in table 2. *$P<0.05$.

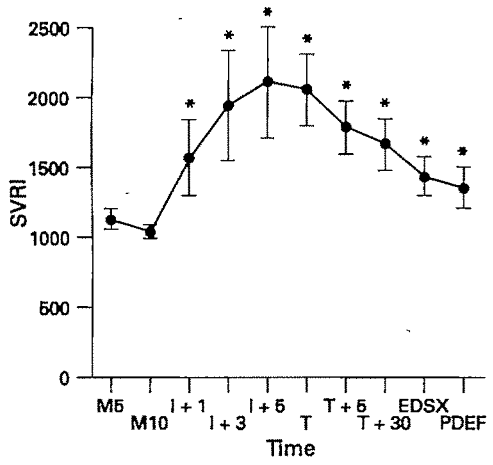

*Figure 3* Index of systemic vascular resistance (SVRI) (mean, SEM; $n=10$) during laparoscopic hernia repair. Times are those shown in table 2. *$P<0.05$.

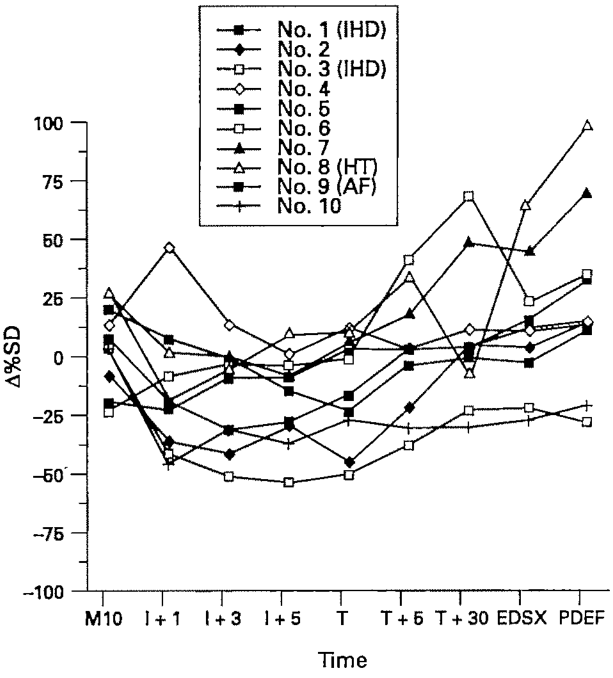

*Figure 4* Percentage change in oesophageal Doppler stroke distance (Δ%SD) from baseline (time M5) for 10 patients during laparoscopic hernia repair. Times are those shown in table 2 Patient numbers correspond to data shown in table 2. Patients with ischaemic heart disease (IHD), hypertension (HT) or atrial fibrillation (AF) are indicated.

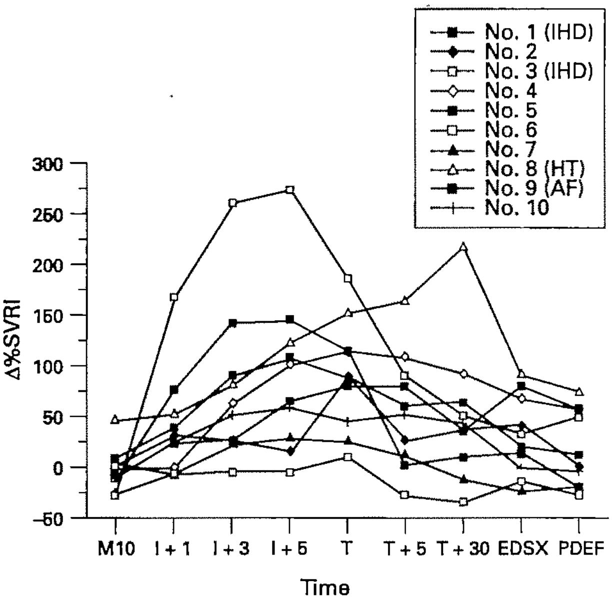

*Figure 5* Percentage change in systemic vascular resistance index (Δ%SVRI) from baseline for 10 patients during laparoscopic hernia repair. Times are those shown in table 2. Patient numbers correspond to data shown in table 2. Patients with ischaemic heart disease (IHD), hypertension (HT) or atrial fibrillation (AF) are indicated.

(table 3). During Trendelenburg positioning both minute distance and stroke distance started to increase towards pre-inflation values but SVRI remained significantly increased ($P<0.05$) compared with baseline values, even after deflation of the abdomen. There were no significant changes in heart rate and oxygen saturation throughout the procedure.

Patient No. 8 had a profound decrease in MAP on induction of anaesthesia (from 117 to 60 mm Hg) which was treated with ephedrine 6 mg. MAP increased progressively after this but did not reach pre-induction levels. Patient Nos 1 and 8 had episodes of multifocal ventricular ectopics which resolved without treatment and without new ECG

*Table 3* Heart rate (HR), minute distance (MD), oxygen saturation ($Sp_{O_2}$), end tidal carbon dioxide partial pressure ($PE'_{CO_2}$) and peak airway pressure (PAP) during laparoscopic hernia repair (mean (SEM)). Times are those shown in table 2. *$P<0.05$

| | | Time | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Preop. | M5 | M10 | I+1 | I+3 | I+5 | T | T+5 | T+30 | EDSX | PDEF |
| HR (beat min$^{-1}$) | 64.3 | 60.7 | 62.5 | 65.1 | 67.6 | 67.5 | 68.0) | 62.6 | 63.3 | 64.6) | 61.4 |
| | | (2.9) | (4.0) | (3.8) | (4.9) | (5.5) | (6.0) | (5.1) | (4.7) | (5.1) | (4.1) |
| MD (cm) | | 747.5 | 748.5 | 595.5* | 601.1* | 595.6* | 626 7* | 677.0 | 761.8 | 786.2 | 837.9 |
| | | (82.1) | (82.1) | (50.1) | (47.3) | (49.2) | (57.2) | (69.9) | (89.9) | (72.0) | (85.8) |
| $Sp_{O_2}$ (%) | 96.8 | 97.6 | 97.7 | 97.6 | 97.6 | 97.6 | 97.4 | 97.3 | 96.1 | 96.2 | 96.2 |
| $PE'_{CO_2}$ (kPa) | | 4.4 | 4.3 | 4.4 | 4.6 | 4.7 | 5.1* | 5.4* | 5.8* | 5.9* | 6.2* |
| | | (0.09) | (0.13) | (0.09) | (0.13) | (0.09) | (0.09) | (0.13) | (0.25) | (0.32) | (0.32) |
| PAP (cm $H_2O$) | | 19.4 | 20.1 | 24.9* | 25.1* | 25.7* | 27.1* | 27.4* | 27.4* | 27.3* | 20.4 |
| | | (1.2) | (1.4) | (2.3) | (2.3) | (2.0) | (2.1) | (2.2) | (2.2) | (2.0) | (1.5) |

changes after operation. Patient No. 7 had an episode of hypotension 2 h after operation associated with bradycardia which was treated successfully with fluids and glycopyrronium and he also made an uneventful recovery.

## Discussion

We have used oesophageal Doppler for non-invasive haemodynamic monitoring during laparoscopic hernia repair. Despite maintaining a relatively low intra-abdominal pressure (<13 mm Hg) throughout the procedure, significant haemodynamic changes were seen. Group trends were similar to those described during pneumoperitoneum by other investigators: a relatively stable heart rate in association with an increase in MAP, decrease in indices of cardiac output and increase in the index of systemic vascular resistance during insufflation of the abdomen with carbon dioxide.[9] Inter-patient variation in cardiovascular response to insufflation of the abdomen with carbon dioxide and assumption of the Trendelenburg position was marked. This degree of variation in our small group of 10 patients suggests the need for close monitoring during laparoscopic procedures in this patient population.

Ten consecutive patients undergoing intraperitoneal laparoscopic inguinal hernia repair were selected regardless of age and medical status. Four of the group had coexistent cardiovascular disease and the changes seen in these patients were more marked than in those patients without cardiovascular disease, particularly the increase in SVRI. This subgroup with cardiovascular disease also showed greater haemodynamic variability in response to induction of anaesthesia and insufflation of the abdomen. It is not clear if this was related to underlying cardiovascular insufficiency or to cardiac medication. The anaesthetic technique was selected to provide cardiovascular stability but systemic arterial pressure decreased in all patients after induction of anaesthesia and it may have been preferable to wait longer before recording baseline variables. We made no attempt to control the fluids administered, although no patient received more than 15 ml kg$^{-1}$ of Hartmann's solution.

The oesophageal Doppler has been used extensively to monitor cardiac output and other variables in healthy subjects and critically ill patients.[8] Good agreement has been shown with thermodilution techniques.[10] In the oesophageal position, excellent signals are obtained from blood travelling through the adjacent descending aorta thereby providing continuous beat-by-beat monitoring with little artefact. The probe is easy to position and signals can be interpreted without specialist training. Waveform changes frequently preceded changes in arterial pressure or heart rate and appeared to provide earlier warning of haemodynamic deterioration.

Disadvantages of oesophageal Doppler include a small risk of injury to the pharynx and oesophagus and a requirement for anaesthesia so that prolonged postoperative monitoring may be difficult. Although probe position mostly remains stable, repositioning is occasionally required. Haemodynamic measures using this technique depend on several assumptions. It is assumed that the angle of incidence of the ultrasound beam to the direction of blood flow is the same as that of the probe face to the long axis of the instrument and that blood flow in the descending aorta remains in fixed proportion to total left ventricular output over wide ranges of flow, pressure and temperature.[7] Under resting conditions the validity of these assumptions has been supported by experimental data, but during insufflation of the abdomen, the distribution of aortic blood flow may vary and a greater percentage of cardiac output may be diverted to the head and upper body as regional afterload is altered.

Pulmonary artery catheterization has been used for haemodynamic monitoring during laparoscopic procedures.[11] This technique permits more precise calculation of left ventricular preload, afterload and oxygen delivery, which may be useful in high-risk cases. The pulmonary artery catheter may also be inserted before induction of anaesthesia and retained after operation for prolonged monitoring. These advantages must be weighed against a low but appreciable risk of morbidity which may not be appropriate for the majority of patients. Oesophageal Doppler appears to offer a safer alternative with the added benefit of continuous online display which is particularly suitable for monitoring acute haemodynamic changes.

There is no doubt that insufflation of the abdomen with carbon dioxide produces measurable effects on the cardiovascular system but the clinical significance of these is uncertain. Insufficient morbidity and mortality data are available to determine if invasive monitoring affects outcome in high-risk patients undergoing laparoscopic surgery. Extending the scope of laparoscopic techniques to older groups of patients at higher risk of cardiovascular complications requires reappraisal of haemodynamic monitoring during anaesthesia.

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*British Journal of Anaesthesia* 1997; **78**: 520–523

# Transcranial cytokine gradients in patients requiring intensive care after acute brain injury

E. G. McKeating, P. J. D. Andrews, D. F. Signorini and L. Mascia

**Summary**

After acute brain injury there may be increased intracranial production of cytokines, with activation of inflammatory cascades. We have sought to determine if a transcranial cytokine gradient was demonstrable in paired sera of 32 patients requiring intensive care after acute brain injury. The difference between concentrations of IL-1β, IL-6, IL-8 and TNFα in jugular venous and arterial serum was measured on admission, and at 24, 48 and 96 h after the primary injury. There were no differences in IL-1β, IL-8 or TNFα, but median gradients of 6.7 and 11.5 pg $ml^{-1}$ for IL-6 were demonstrated in the traumatic brain injury ($n$=22) and subarachnoid haemorrhage ($n$=10) groups, respectively (normal values in serum <4.7 pg $ml^{-1}$; $P<0.001$ both groups). This suggests that there is significant production of IL-6 by intracranial cells after acute brain injury. Therapy directed towards combatting the negative effects of IL-6 may potentially benefit patients who have sustained an acute brain injury. (*Br. J. Anaesth.* 1997; **78**: 520–523).

**Key words**
Brain, injury. Polypeptides, cytokines. Intensive care.

The cytokines are a variety of polypeptide molecules which function as mediators within the communication network of the immune system.[1] They have been implicated in the pathophysiology of many disease processes, including the systemic inflammatory response syndrome (SIRS),[2] acute respiratory distress syndrome (ARDS)[3] and multiple trauma.[4] Many of the biological effects of the cytokines are clinically evident after acute brain injury; these include neutrophilia, pyrexia and alteration of endothelial permeability,[5] which may result in cerebral oedema,[6] as a result of disruption of blood–brain barrier function.

Increased concentrations of serum tumour necrosis factor-α (TNFα),[7] interleukin-6 (IL-6)[8] and intraventricular fluid IL-6 and IL-1β[9] have been demonstrated after traumatic brain injury, and experimental work has demonstrated that glial cells are able to manufacture cytokines.[10 11] After acute brain injury it has been suggested that increased intracranial production of pro-inflammatory cytokines, with consequent induction of auto-destructive inflammatory cascades, results in secondary injury to the brain, causing altered brain metabolism and cell death.[12] With the increased use of intra-parenchymal solid state methods for monitoring intracranial pressure, access to cerebrospinal fluid for analysis is often not possible, and where it is, sampling from catheters may result in ventriculitis.[13] Insertion of a fibreoptic catheter into the jugular bulb to monitor jugular venous haemoglobin oxygen saturation is now standard practice within our intensive care unit (ICU) in acute brain injured patients, giving ready access to blood draining from the brain.[14] We investigated the hypothesis that systemic concentrations of the cytokines IL-1β, IL-6, IL-8 and TNFα are increased after acute brain injury, and that increased intracranial production of these cytokines results in a demonstrable transcranial cytokine gradient, with jugular venous concentrations higher than arterial concentrations.

## Patients and methods

After obtaining local Ethics Committee approval, we studied 32 patients who had sustained an acute brain injury (traumatic brain injury (TBI) or spontaneous subarachnoid haemorrhage (SAH)) requiring intensive care. Patient data consisting of sex, age, and Glasgow coma score (GCS) after non-surgical resuscitation were recorded on admission to the ICU (see table 1). One patient whose initial GCS was recorded as 15 was anaesthetized at the scene soon after injury because of flail chest. Computerized tomography (CT) subsequently demonstrated severe traumatic brain injury.

A dual-lumen Edslab 4-French gauge oximetry catheter (Baxter Healthcare Corporation, Irvine, CA, USA) was inserted into the jugular bulb on the dominant side of the cerebral venous drainage, as described previously.[15 16] Satisfactory positioning was ensured by lateral x-ray of the cervical spine (catheter tip seen cephalad to the upper border of the C2 vertebral body), and the correct catheter distance marking (e.g. 15 cm) showing at the valve of the sheath was written in the notes for future

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*Table 1* Characteristics of patient population (median (range)). The characteristics of the subset, including only the first 20 patients, are shown in parentheses

| | TBI group ($n$=22 (12)) | SAH group ($n$=10 (8)) |
|---|---|---|
| Sex (M/F) | 18/4 (9/3) | 6/4 (4/4) |
| Age (yr) | 34 (35)<br>17–69 (17–49) | 52 (51.5)<br>21–65 (21–65) |
| GCS | 7 (7)<br>3–15 (3–15) | 7 (7)<br>5–10 (5–10) |

*Table 2* Performance characteristics of each assay. To assess intra-assay precision, three samples of known concentration were assayed 20 times on one plate. To assess inter-assay precision, three samples of known concentration were assayed in 20 separate assays

| | Intra-assay coefficient of variation (%) | | | Inter-assay coefficient of variation (%) | | |
|---|---|---|---|---|---|---|
| Sample | 1 | 2 | 3 | 1 | 2 | 3 |
| IL-1β | 3.4 | 4.4 | 2.8 | 8.4 | 4.2 | 4.1 |
| IL-6 | 4.3 | 1.7 | 2.1 | 6.3 | 3.3 | 7.2 |
| IL-8 | 3.9 | 2.4 | 3.3 | 12.2 | 9.1 | 7.3 |
| TNFα | 5.2 | 4.2 | 4.6 | 7.4 | 4.6 | 5.4 |

reference. An intra-arterial catheter was inserted (if not already *in situ*), usually in the radial artery, as is our standard practice.

Paired arterial and jugular venous blood samples were obtained at designated times after brain injury: within 12 h (median 8 h 30 min, range 2–14 h), and at 24, 48 and 96 h. Time of brain injury in the SAH group was noted as the time of sudden deterioration in GCS by 3 points or more. Patients who did not exhibit sudden neurological deterioration were not included. The diagnostic criterion for SAH was the presence of subarachnoid blood on the CT scan. Satisfactory positioning of the jugular bulb catheter was ensured before each sample was obtained by checking that the correct distance marker of the catheter was showing at the sheath valve. Samples were allowed to clot at room temperature, spun down in a centrifuge at 4000 rpm for 10 min and the supernatant removed and frozen immediately at −25 °C. Analysis of serum for IL-1β, IL-6, IL-8 and TNFα was performed by enzyme-linked immunosorbent assay (Quantikine Human Cytokine Assays, R&D Systems) according to the manufacturer's instructions. Inter- and intra-assay coefficients of variation for each assay are shown in table 2. All analyses were carried out by a single operator using the same equipment and procedures throughout. Repeat freeze–thaw cycles for serum samples were avoided by separating the serum from each patient into four tubes before freezing.

A total of 138 samples (69 pairs) were analysed in duplicate for each cytokine (with an additional 80 samples for IL-6) and results averaged to give the final concentration. Samples which gave a result higher than the highest standard supplied with the kit were diluted and the assay repeated. Sera from eight healthy volunteers were analysed as controls. Standard curves and cytokine concentrations were calculated on a personal computer interfaced to a micro-plate reader using dedicated software (Bio-Rad Laboratories). Statistical analysis was by Wilcoxon rank sum and signed rank tests using Splus for Windows 3.2.

## Results

In 119 of the 138 samples assayed for IL-1β (86%), concentrations were undetectable (<3.9 pg ml$^{-1}$). The highest concentration in the remaining 19 (14%) was 7.0 pg ml$^{-1}$. For TNFα, in 122 samples (88%) concentrations were undetectable (<15.6 pg ml$^{-1}$). The highest concentration in the remaining 16 (12%) was 31 pg ml$^{-1}$. IL-8 was detected in 72 samples (52%) (lower limit of detection 94 pg ml$^{-1}$), but only 10 (7%) showed concentrations >300 pg ml$^{-1}$. There was no difference between jugular venous and arterial concentrations of IL-1β, IL-8 or TNFα in those patients

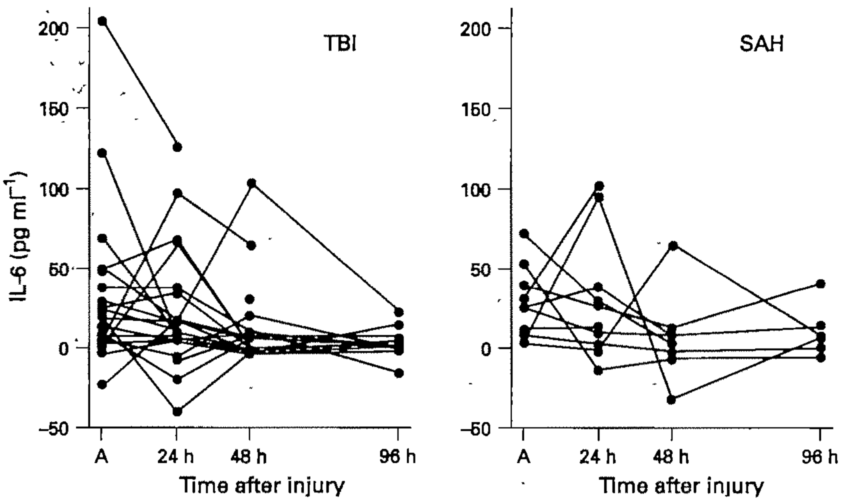

*Figure 1* Differences between jugular venous and arterial concentrations of IL-6 in traumatic brain injury (TBI, $n$=22) and spontaneous subarachnoid haemorrhage (SAH, $n$=10), over a 4-day period after injury (A=admission). Data may be incomplete because of patient death, discharge from ICU or values lying outside ELISA quantification values. For the TBI group, at each time, $n$=20, 21, 19 and 11, respectively; for the SAH group, $n$=10, 10, 8 and 6, respectively.

with detectable concentrations. Control samples all showed undetectable concentrations.

IL-6 was detected in all 218 samples. In the controls, concentrations were below detectable limits (<3.1 pg ml$^{-1}$) in four samples. The highest concentration in the remaining four control samples was 4.7 pg ml$^{-1}$. In four pairs of patient samples (3.7%), both samples showed concentrations >1500 pg ml$^{-1}$ (the upper limit of quantification) and were excluded from statistical analysis. In 82 (78.1%) of the remaining 105 pairs, jugular venous concentration was higher than arterial. In the TBI group, median jugular venous concentration was 74.8 (range 19.9–539.8) pg ml$^{-1}$), median arterial concentration was 63.5 (11.4–518.4) pg ml$^{-1}$ and the median difference was 6.7 (−40.8 to 244.4) pg ml$^{-1}$ ($P<0.001$). In the SAH group, median jugular venous concentration was 64.6 (19.1–455.4) pg ml$^{-1}$, median arterial concentration was 54.1 (12.2 to 407.4) pg ml$^{-1}$ and the median difference was 11.3 (−32 to 135.2) pg ml$^{-1}$ ($P<0.001$).

Figure 1 shows the individual patient profiles for transcranial IL-6 gradient for each group. In the TBI group, median gradients at each time point were 19.2 ($P<0.001$), 10.5 ($P=0.014$), 6.3 ($P=0.018$) and 1.6 pg ml$^{-1}$ ($P=0.147$), respectively. In the SAH group, median gradients were 26.8 ($P=0.002$), 20.1 ($P=0.027$), 5.6 ($P=0.383$) and 7.8 pg ml$^{-1}$ ($P=0.094$), respectively. Comparing the TBI and SAH groups, there was a significant difference in age between the groups ($P=0.028$), but there was no difference in GCS ($P=0.979$). There was no overall difference in IL-6 gradients across the brain between the TBI and SAH groups ($P=0.350$); there were no differences between groups at any of the four sampling times ($P=0.559$, 0.627, 0.832, 0.366, respectively).

## Discussion

We were unable to derive any useful information from measurement of either arterial or jugular venous serum concentrations of IL-1β, IL-8 or TNFα at these times after acute brain injury. It is generally believed that IL-1β and TNFα are released in the early post-injury phase,[17,18] resulting in increased synthesis of IL-6, in addition to other mediators. IL-6 may act to decrease production of IL-1β and TNFα via a negative feedback mechanism.[19] It may be that we missed an early peak of production of IL-1β and TNFα before the patients reached the ICU. The relatively high lower limit of detection for IL-8 (94 pg ml$^{-1}$) in this particular assay may have masked any significant transcranial gradient.

Results for IL-6 show increased jugular venous concentrations of this cytokine relative to arterial concentrations, particularly within 48 h of brain injury. Transcranial gradients in the TBI and SAH groups were similar, despite different aetiologies of primary injury, suggesting that the mechanisms of the inflammatory process may be similar. The median transcranial gradient on admission in each group was 5–6 times higher than the highest systemic concentration measured in the controls. This suggests significant intracranial production of IL-6. The source of this increased production is likely to be glial cells, and there is experimental evidence to suggest that both astrocytes[10] and microglial cells[11] may be involved. In addition, systemic concentrations of IL-6 were increased greatly. This may be caused solely by intracranial production, but is much more likely to be a result of release of IL-6 from extracranial sources, that is a mild SIRS. Variation in systemic concentrations of IL-6, jugular venous–arterial differences, and different patterns of concentration gradients seen over time may be related to the severity of intracranial injury, type of injury, presence of extracranial injuries or secondary insults to the brain while in the ICU.

This pattern of prolonged elevation of IL-6 is seen in SIRS and ARDS, and serum concentrations of IL-6 have been shown to be related to outcome in these conditions, both in terms of maximum concentrations detected[20] and persistence of IL-6 in serum over time.[21,22] There has been little work relating outcome in acute brain injury to IL-6 concentrations in serum. We are presently collecting outcome data for our group of patients.

A study which compared post-mortem appearances of the brains of non-survivors of traumatic brain injury in Glasgow over two periods (1968–1972 and 1981–1982) showed that the incidence of ischaemic damage had not changed, despite improved intensive care in this group of patients.[23] Analysis of our own secondary insult database of physiological variables for acute brain injured patients in the ICU revealed a significant reduction in hypotensive and hypoxic insults (i.e. periods where mean arterial pressure and arterial haemoglobin oxygen saturation decreased to below acceptable limits) to the brain over a 7-yr period, but this has not been parallelled by a similar reduction in mortality. We can speculate that in inflammatory disease states the mediators produced may prevent cells from using oxygen supplied to tissues, that is there exists a state of histotoxic hypoxia. This may explain why therapeutic efforts directed at increasing oxygen delivery to tissues have not resulted in improved outcome in SIRS.[24,25] If this hypothesis is correct then a different therapeutic approach is necessary.

Future management of acute brain injured patients may include pharmacological modification of the inflammatory processes involved in the pathophysiology of the condition, using antibodies or receptor antagonists, preventing further cell death and improving outcome.

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# Ketamine increases the amplitude of the 40-Hz auditory steady-state response in humans†

G. PLOURDE, J. BARIBEAU AND V. BONHOMME

## Summary

The auditory middle latency response (AMLR) and the 40-Hz auditory steady-state response (40-Hz ASSR) are evoked potentials which possibly arise from the same generators in the primary auditory cortex. Both responses are attenuated by most general anaesthetics. Ketamine, however, has been reported to have no effect on the AMLR. Our aim was to evaluate the effects of ketamine on the 40-Hz ASSR. Spectral analysis of the electroencephalogram (EEG) was also conducted to independently examine the effects of ketamine. Ketamine 1.5 mg $kg^{-1}$ was given to 12 patients for induction of general anaesthesia. Recordings of the 40-Hz ASSR and EEG were obtained every minute from 3 min before administration of ketamine to 5 min after injection, when the study was terminated. Similar recordings were obtained in three control subjects under identical conditions except that no medication was administered. Consciousness, defined as responsiveness to verbal commands, was assessed before each recording. Ketamine caused an *increase* in the amplitude of the 40-Hz ASSR ($P<0.01$). Using published AMLR data, we conducted a simulation experiment that suggested that the effect of ketamine on the AMLR can explain its effects on the amplitude of the 40-Hz ASSR. There was a pronounced increase in relative theta (3.9–7.9 Hz) EEG power and a decrease in relative alpha (8.0–12.8 Hz) power ($P<0.001$). These changes were not observed in the control group. Ketamine produced unconsciousness until the end of the study in five patients and transient unconsciousness in five patients. Two patients did not lose consciousness after administration of ketamine. The 40-Hz ASSR and EEG revealed no consistent differences between conscious and unconscious patients. No relationship could be demonstrated between the increase in amplitude of the 40-Hz ASSR or of relative theta power (the hallmark of ketamine effect) and loss of responsiveness to commands. We conclude that ketamine, unlike other anaesthetics, *increases* the amplitude of the 40-Hz ASSR. (*Br. J. Anaesth.* 1997; **78**: 524–529).

**Key words**

Anaesthetics i.v., ketamine. Brain, evoked potentials. Monitoring, evoked potentials. Anaesthesia, depth.

The auditory middle-latency response (AMLR)[1] and the 40-Hz auditory steady-state response (40-Hz ASSR)[2] are affected by general anaesthetics. Both responses are auditory evoked potentials, that is changes in the electrical activity of the brain caused by auditory stimuli. The AMLR and the 40-Hz ASSR probably arise from the same generator in the primary auditory cortex.[3] Differences between the two responses depend on the rate of stimulus delivery. The AMLR is a *transient* evoked response. Transient responses are evoked by stimuli presented at a rate sufficiently slow so that the response to one stimulus is over before the next stimulus occurs. The 40-Hz ASSR is a *steady-state* response. Steady-state responses are evoked by stimuli presented so rapidly as to cause overlapping of the responses to successive stimuli.[4]

Schwender and colleagues[5] recently examined the effect of ketamine 2 mg $kg^{-1}$ on the AMLR during induction of general anaesthesia. They concluded that ketamine had no effect on the AMLR. The effects of ketamine on the 40-Hz ASSR have not been studied. The aim of this study was to measure the effect of ketamine 1.5 mg $kg^{-1}$ on the 40-Hz ASSR. It was not possible to concurrently record the AMLR but the EEG was recorded to document independently the effects of ketamine.

## Patients and methods

The study was approved by the institutional Ethics Committee. We studied 12 ASA I elective surgical patients, aged 18–50 yr (mean 33 yr), who gave written informed consent. All were within the ideal body weight range (Metropolitan Weight Tables, 1983), denied past neurological or otological disease and had normal otoscopy. No premedication was given. After insertion of an i.v. cannula into the left arm and placement of monitors (ECG, arterial pressure cuff and pulse oximetry probe) patients breathed oxygen by face mask for 3 min. Three

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baseline recordings of the 40-Hz ASSR were obtained, one every minute. Ketamine (Ketalar) 1.5 mg $kg^{-1}$ was given over 15 s and the 40-Hz ASSR recorded every 1 min for 5 min, starting with the beginning of injection. Before each recording the level of consciousness was assessed by asking the patient to squeeze the fingers of an observer unaware of the 40-Hz ASSR results. A patient who obeyed was considered conscious.

At 5 min after administration of ketamine, the study was terminated. Midazolam 0.1 mg $kg^{-1}$ and thiopentone 3 mg $kg^{-1}$ were given before proceeding with standard anaesthetic care. While in the recovery room after surgery, patients were asked to describe what they remembered from the induction period.

To verify the stability of the responses, recordings were obtained in three volunteers (aged 30–40 yr) under identical conditions except that the i.v. cannula was only taped to the skin, rather than inserted into a vein, and no medication was administered.

A microcomputer (Intel 80386 processor) was used for controlling stimulus delivery and recording the electroencephalogram (EEG). Stimuli were 500 Hz tonebursts (10 ms duration; 2 ms rise and fall time; 84 dB peak equivalent sound pressure level) delivered binaurally at a rate of 40 $s^{-1}$ via insert earphones ("E-A-R TONE" 3A, Cabot Corporation, Indianapolis, IN, USA). The stimulus waveform (gated continuous sine wave) was created by the microcomputer, fed through a digital-to-analogue (D/A) converter (D/A rate 20 kHz) and attenuated before reaching the earphones to obtain 84 dB.

The EEG was recorded from Cz[6] with gold-plated cup electrodes filled with conductive gel. The reference was the right mastoid and the ground was on the back of the neck over the fifth cervical vertebra. Impedances were maintained at less than 3 kΩ (at 30 Hz). The EEG was amplified (amplifier model 12A5, Grass Instruments Co., Quincy, MA, USA) with a bandpass of 0.3–100 Hz. The analogue-to-digital (A/D) sampling rate was 298.978 Hz with 1024 data points per channel, yielding an epoch duration of 3.425 s. The A/D resolution was 12 bits. Epochs contaminated by excessive artefacts were rejected. The criterion for rejection was 10% or more data points exceeding +100 μV. Epochs were averaged by groups of 10.

## MEASUREMENTS

### *40-Hz ASSR*

Amplitude (baseline to peak) and phase (sine function) at 40 Hz were obtained by computing the fast Fourier transform (FFT)[7] of the averaged waveforms. No windowing was used because the choice of the sampling frequency ensured that there would be an FFT term exactly at 40 Hz.

### *EEG*

Because averaging uniformly attenuates all frequencies, it is possible to obtain an estimate of the power spectrum of the EEG from the averaged waveforms.[8] The presence of evoked activity (40-Hz ASSR) does not interfere with this process, because it is outside the frequency range used for EEG analysis.[8] Power from 30.0 to 38.0 Hz and from 42.0 to 50 Hz was first measured to estimate absolute gamma band power. The 38.0–42.0 Hz range was omitted to avoid contamination by the 40-Hz ASSR. A non-phase shift FFT-based digital filter[7] was used to remove residual noise below 1.5 Hz and above 30 Hz. The power spectrum of the averaged waveforms was computed by FFT with a Hanning window. Absolute power in the following frequency bands was measured: delta (1.5–3.8 Hz), theta (3.9–7.9 Hz), alpha (8.0–12.8 Hz), beta 1 (12.9–19.9 Hz) beta 2 (20.0–30.0 Hz) and gamma (30.0–38.0 Hz and 42.0–50 Hz). Relative power for each band was obtained by dividing absolute power by total power (1.5–30 Hz plus gamma band).

## STATISTICAL ANALYSIS

When required, data were log transformed to meet the normality assumption (Lilliefors test).[9] Analysis of variance (ANOVA) for repeated measures with six levels (baseline, the average of the three baseline recordings and the 0-, 1-, 2-, 3- and 4-min recordings) was used. The least significant difference (LSD) test was used for planned *post hoc* comparison (baseline *vs* each subsequent recording).[10] The Pearson product moment correlation coefficient[11] was used to evaluate the relationships between variables at each assessment time. The Lilliefors test was carried out with the program Systat (version 5.2.1 for Macintosh) (SPSS Inc, Chicago, IL, USA). All other procedures were carried out with CSS Statistica (version 3.1 for DOS) (Statsoft Inc, Tulsa, OK, USA). The criterion for significance was $P<0.01$. All differences approaching significance ($0.01<P<0.05$) are indicated.

## PREDICTING THE EFFECTS OF KETAMINE ON THE 40-HZ ASSR FROM ITS EFFECTS ON THE AMLR

It is reasonable to assume that in awake subjects the 40-Hz ASSR can be predicted from the AMLR by superposition.[12–14] It was not possible to concurrently record the AMLR. The effects of ketamine 2 mg $kg^{-1}$ on the AMLR have been described by Schwender and colleagues.[5] Although these authors found no change in the amplitude and latencies of the peaks of the AMLR, inspection of their waveforms suggests that ketamine enhanced near 40-Hz oscillations occurring 40–80 ms after the stimulus. We have used the data of Schwender and colleagues[5] to study the effect of ketamine on the amplitude of the 40-Hz ASSR.

Figures 1 and 2 from Schwender and colleagues[5] were digitized with a flat-bed high resolution (600 dpi) scanner. The resulting bitmap images were traced manually with Corel Draw (version 2.0, Corel Draw Corporation, Ottawa, Canada). Each traced waveform was exported as a HPGL (Hewlett-Packard graphics language) file.[15] The HPGL file contains the X-Y coordinates of the waveform. Cubic spline interpolation[7] was used to obtain measurements from 0 to 99 ms in 1-ms steps. Visual inspection showed that the recovered waveforms were virtually identical to the originals from the article by Schwender and colleagues.[5] The predicted 40-Hz ASSR waveform was computed from the recovered AMLR by summation of the four 25-ms segments of the AMLR (0–24, 25–49, 50–74 and 75–99 ms) (See Plourde and Villemure[16] for a complete description of the computation.) The amplitude of the predicted ASSR was obtained by FFT.

## Results

### 40-HZ ASSR

There was a decrease in amplitude for the recording started concurrently with administration of ketamine ($t=0$ min, $P<0.05$) followed by a progressive increase in amplitude ($P<0.01$ at $t=3$ min) (table 1, fig. 1). For phase, there was a sudden increase for the recording started 1 min after administration ($P<0.001$). Phase remained significantly higher than baseline afterwards, despite a progressive decline towards baseline values (table 1, fig. 1). The control subjects showed no amplitude or phase changes with time.

### EEG

Three variables showed significant changes after administration of ketamine: relative power in the alpha, beta 1 and theta frequency bands (table 1, fig. 2). There was a significant ($P<0.001$) decrease in relative alpha power for the recording started 3 min after injection. Relative beta 1 power also decreased significantly ($P<0.01$) from 1 min onwards after injection. There was a very pronounced and highly significant ($P<0.001$) increase in relative theta power from 1 min after injection. Relative alpha and theta power remained stable over time in the three control subjects. Relative beta 1 power however decreased by approximately 30% in the controls (compared with approximately 50% in patients).

There was a modest decrease in relative delta power after ketamine but the difference was not significant ($P=0.18$, ANOVA). Relative power in beta 2 and gamma bands remained stable over time in patients and control subjects (fig. 2).

*Table 1* Outcome of statistical analysis. I=Increase, D=decrease. *$P<0.05$, **$P<0.01$, ***$P<0.001$

| | 40-Hz ASSR | | EEG relative power | | |
|---|---|---|---|---|---|
| | Amplitude | Phase | Alpha | Beta 1 | Theta |
| ANOVA | ** | $<10^{-4}$ | ** | *** | $<10^{-4}$ |
| Planned comparison: baseline *vs* recording started at | | | | | |
| 0 min | D* | | | | |
| 1 min | | I*** | | D** | I*** |
| 2 min | | I*** | | D** | I*** |
| 3 min | I** | I*** | D*** | D*** | I*** |
| 4 min | I* | I** | D* | D*** | I*** |

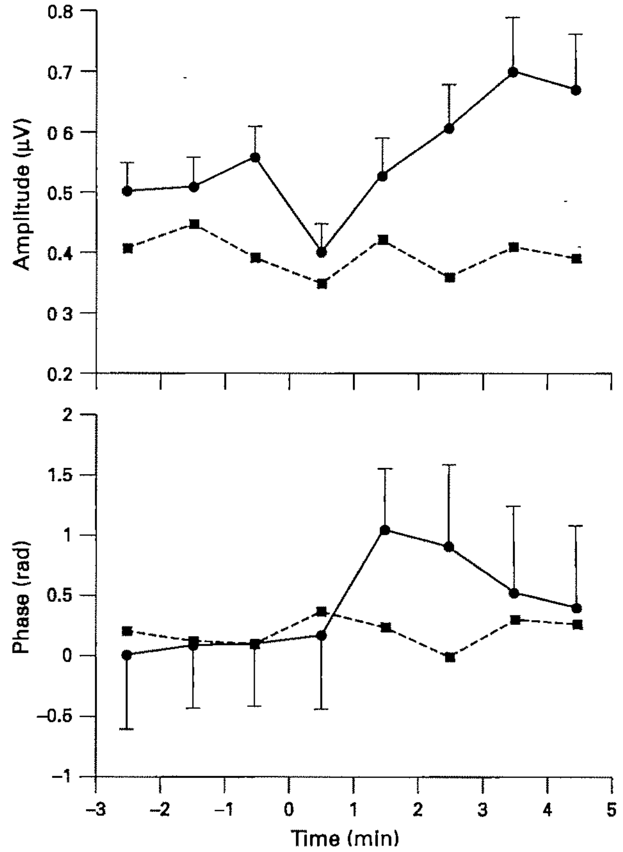

*Figure 1* Amplitude and phase of the 40-Hz ASSR. ●=Mean, SEM for patients ($n=12$); ■=mean for control subjects ($n=3$). Each datum point represents 34.25–47.95 s (depending on the number of rejected epochs, 0–4) of recording time, starting at the beginning of the interval where the point is plotted. Ketamine was given at time 0.

### RESPONSIVENESS TO VERBAL COMMANDS

Responsiveness to verbal commands was assessed *before* each recording. All patients were responsive for the baseline recordings and for recording during which ketamine was administered. Five patients became unresponsive for the four recordings started after administration of ketamine. Two patients remained responsive for all recordings after injection. Five patients remained responsive for one or two of the four recordings after injection. There were no differences between the five patients who remained unresponsive during all recordings after injection and two patients who remained responsive throughout, with regard to amplitude (fig. 3) and phase of the 40-Hz ASSR or to any EEG variables. Even during unresponsiveness to commands, patients' eyes frequently remained intermittently open and the eyelash reflex to touch was present. No patient had any recollection of events after administration of ketamine.

### PREDICTED 40-HZ ASSR FROM THE AMLR DATA OF SCHWENDER AND COLLEAGUES[5]

The amplitude of the predicted 40-Hz ASSR is shown in table 2. The 40-Hz ASSR predicted from the grand average waveforms from Schwender and colleagues[5] (their fig. 2, based on 20 patients) was

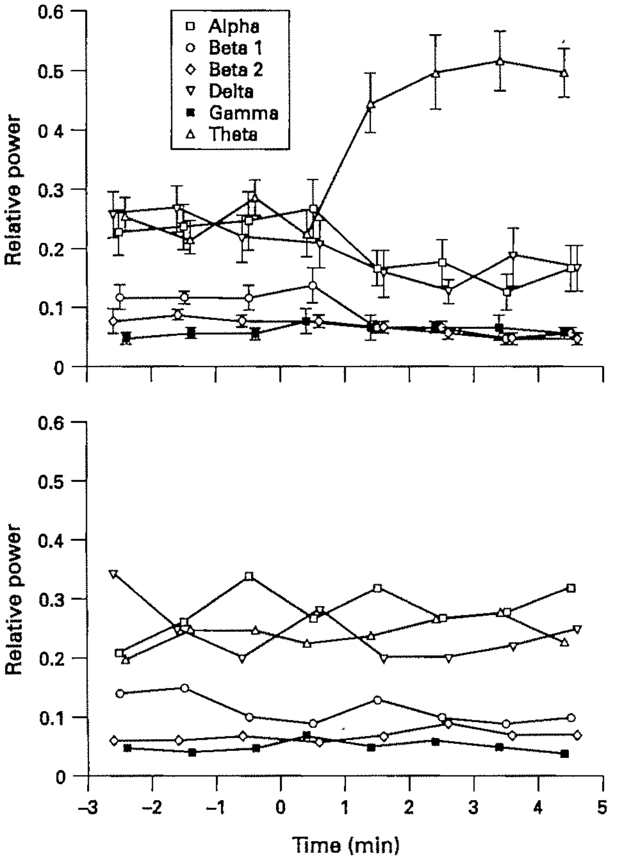

*Figure 2* Relative power for each frequency bands. Each datum point represents 34.25–47.95 s (depending on number of rejected epochs), starting at the beginning of the interval where the point is plotted. Ketamine was given at time 0. A small horizontal offset was used for clarity. Top: results for patients ($n$=12; mean, SEM); bottom: results for controls ($n$=3; mean only because of small sample size).

*Table 2* Relative amplitude of the 40-Hz ASSR predicted from the data reported by Schwender and colleagues.[5] The grand average data are from their figure 2. Patients 1–4 are from their figure 1, with patients numbered clockwise

| | Grand average | Patient No. 1 | Patient No. 2 | Patient No. 3 | Patient No. 4 |
|---|---|---|---|---|---|
| Baseline | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 0–2 min | 1.42 | 1.15 | 1.75 | 1 15 | 1.95 |
| 2–4 min | 1.25 | 0.99 | 1.67 | 1.09 | 1.48 |
| 4–6 min | 1.50 | 0.78 | 1.53 | 0.55 | 1.20 |

increased by 25–50% for up to 6 min after ketamine. An increase in the amplitude of the predicted 40-Hz ASSR was also noted on the recordings obtained 0–2 min after ketamine for all four patients shown in figure 2 of Schwender and colleagues.[5] A comparable increase was also noted with two of the four patients on the recordings obtained 2–4 min and 4–6 min after ketamine.

## Discussion

Unlike other anaesthetics,[17] ketamine *increased* the amplitude of the 40-Hz ASSR. This observation, though somewhat surprising, was not completely unexpected. The recordings of Schwender and colleagues[5] raised the possibility that ketamine could have a facilitatory role on 40 Hz oscillations after auditory stimuli (see their fig. 2 which shows a new wave occurring 50–70 ms after the stimulus on the recording performed 4–6 min after administration of ketamine). Domino, Chodoff and Corssen[18] observed increased amplitude of the middle latency somatosensory response evoked by electrical

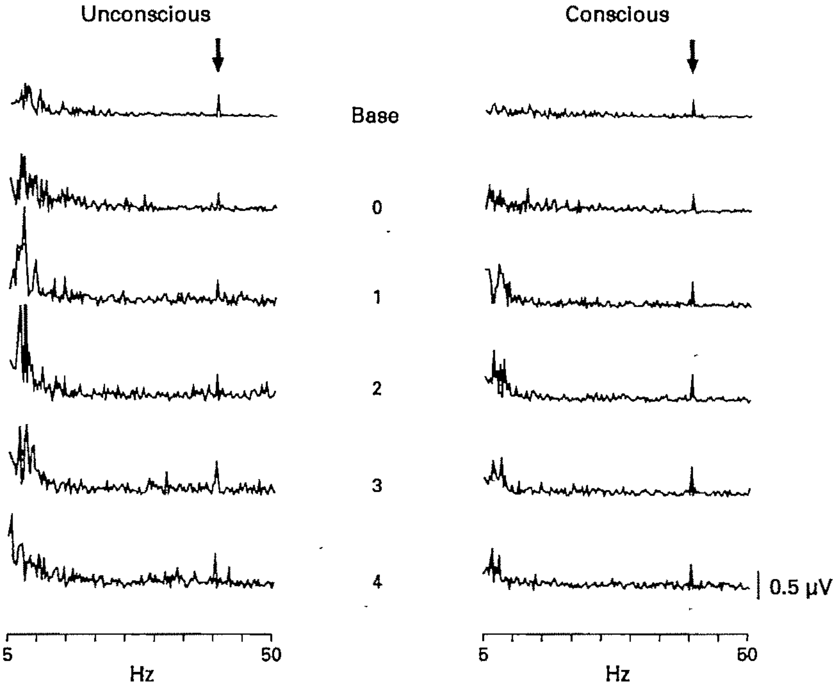

*Figure 3* Amplitude spectra from two patients. The tracings on the left are from a patient who was unconscious before the recordings started, 1–4 min after ketamine. Tracings on the right are from a patient who remained conscious for all recordings. The numbers indicate time (in minutes) when the recording was started relative to administration of ketamine (time 0). The baseline (base) spectra were obtained by computing the fast Fourier transform of the average of the three baseline recordings. The 40-Hz ASSR peak is indicated by the arrows. There was an increase in the 40-Hz amplitude at 3 and 4 min for both patients. Part of low frequency power for the left tracings at 2 min has been clipped to save vertical space.

stimulation of the median nerve. Schultz and colleagues[19] and Schwartz, Virden and Scott[20] showed that ketamine increased spontaneous EEG activity in the 25–45 Hz range. Spontaneous fast (30–40 Hz) rhythms have been recorded during anaesthesia with ketamine and xylazine (an $\alpha_2$ agonist for veterinary use) in thalamocortical networks of cats[21] and in the hippocampus of rats.[22]

Simulation of the 40-Hz ASSR using the data of Schwender and colleagues[5] suggested that the effect of ketamine on the AMLR can explain its effect on the amplitude of the 40-Hz ASSR. The demonstration was particularly convincing for the grand average data from Schwender and colleagues[5] (table 2). An increase in the amplitude of the predicted 40-Hz ASSR was also noted with the four individual subjects from Schwender and colleagues[5] for the recording obtained 0–2 min after administration of ketamine. In two subjects, the increase in amplitude persisted until the last recording, obtained 4–6 min after ketamine. With simulation experiments, we place more emphasis on grand average rather than individual data, because the prediction process works best when there is minimal residual noise. We must acknowledge, however, that the time course of the increase in amplitude of the 40-Hz ASSR observed in this study occurred later than that predicted by the grand average data from Schwender and colleagues.[5] The most likely explanation is the difference in the dose of ketamine between the two studies.

Another possible explanation for the increased 40-Hz ASSR amplitude after ketamine is to view the auditory system as a tuned oscillator[12] with an optimal resonance frequency of 37–38 Hz[23] and to propose that ketamine brings this optimal frequency closer to 40 Hz without changing the AMLR. At present we see no need for this explanation because our reconstruction experiment strongly suggested that the increased 40-Hz ASSR amplitude after ketamine can be explained by superposition of the AMLR.

We did not observe an increase in relative EEG gamma power, as anticipated from the observations of Schultz and colleagues[19] and Schwartz, Virden and Scott.[20] There are two possible explanations. We administered a smaller dose of ketamine (1.5 mg $kg^{-1}$) than Schultz and colleagues (2–3 mg $kg^{-1}$) and Schwartz, Virden and Scott (2 mg $kg^{-1}$). We used averaged EEG traces (based on 10 epochs) for estimation of relative power. Transient modest increases in gamma activity during 2 or 3 epochs would probably be missed by using averages. However, we do not believe that exclusion of the 38–42 Hz range, which contained the 40-Hz ASSR, can explain the absence of the increase in gamma power.

In common with previous investigators, we observed a marked increase in theta power, the hallmark of the EEG effects of ketamine,[18-20] and a decrease in alpha power.[24] The beta 1 power band had not been specifically examined before. We noted a 50% decrease in beta 1 power after ketamine but the three control subjects showed a decrease of 30%. Further observations are required to clarify the effect of ketamine on beta 1 power. This question could perhaps have been resolved if we had studied a larger control group. Our primary motive for testing control subjects was, however, to exclude the remote possibility that the amplitude of the 40-Hz ASSR increases with repeated testing. Because a first group of three control subjects revealed no evidence of amplitude increase with time, we felt that these results were sufficient to confirm the stability of the 40-Hz ASSR and that no further testing with control subjects was required.

A surprising finding was that the above changes of the 40-Hz ASSR and of the EEG were the same whether or not patients remained conscious. This observation differs from the report of Domino, Chodoff and Corssen[18] who indicated that theta activity was present only during unconsciousness, being replaced by fast activity on return of consciousness. Domino, Chodoff and Corssen[18] defined consciousness as the ability to answer questions, a task more complex than following a simple command. The discrepancy between the observations of Domino, Chodoff and Corssen[18] and our own could be explained by the difference in how consciousness was assessed.

Finally, consideration must be given to how ketamine increases the amplitude of the 40-Hz ASSR and spontaneous gamma rhythms. Ketamine is considered a non-competitive antagonist of the *N*-methyl-D-aspartate (NMDA) receptor.[25 26] There is insufficient knowledge of the neurotransmitters involved in generation of the 40-Hz ASSR and spontaneous gamma rhythms to understand why antagonism of the NMDA receptor would enhance these rhythms. Our observations suggest however that the 40-Hz ASSR probably does not depend on NMDA receptors.

We conclude that ketamine, unlike other anaesthetics, increased the amplitude of the 40-Hz ASSR and that this effect can probably be explained by subtle alterations of the AMLR by ketamine.

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# Effects of inotropes on human leucocyte numbers, neutrophil function and lymphocyte subtypes

A. M. BURNS, M. KEOGAN, M. DONALDSON, D. L. BROWN AND G. R. PARK

## Summary

We have investigated the effects of inotropes with different adrenergic receptor specificity on differential white cell count, lymphocyte subtypes and neutrophil function in healthy volunteers. Six healthy, male volunteers were enrolled into this randomized, placebo-controlled pilot study. Each volunteer was studied on four separate occasions during a 2-h infusion of various agents, and for 2 h after stopping the infusion. The agents investigated were adrenaline 0.1 $\mu g\ kg^{-1}\ min^{-1}$, dobutamine 5 $\mu g\ kg^{-1}\ min^{-1}$, dopexamine 2 $\mu g\ kg^{-1}\ min^{-1}$ and 5% glucose 0.5 $ml\ kg^{-1}\ h^{-1}$. Venous blood was sampled at 0, 30, 120 and 240 min. Haemodynamic monitoring was continued throughout the study. Full blood count, white cell differential count and enumeration of lymphocyte subtypes were performed. Neutrophil function tests included chemoluminescence, and assessment of neutrophil chemotaxis, phagocytosis and adhesion. The Wilcoxon signed rank test was used to compare differences between placebo and active drugs at each time compared with baseline. There was a significant increase in white cell count, lymphocyte count and neutrophil count with adrenaline, and a small but significant decrease in these variables with dobutamine and dopexamine. These changes were also apparent for absolute $CD3^+$, $CD4^+$ and $CD8^+$ lymphocyte counts. Neutrophil respiratory burst in response to f-methionyl-leucyl-phenylalanine increased significantly only with adrenaline at 30 min ($P$=0.046). There were no other significant changes in tests of neutrophil function. Infusion of inotropes was associated with changes in white cell numbers, lymphocyte subtypes and neutrophil respiratory burst. In healthy volunteers, adrenaline had effects different from those of dobutamine and dopexamine. The clinical relevance of such effects requires further investigation in critically ill patients. (*Br. J. Anaesth.* 1997; **78**: 530–535).

**Key words**
Blood, leucocytes. Blood, lymphocytes. Blood, neutrophils. Sympathetic nervous system, catecholamines.

There is increasing evidence to suggest that the neuroendocrine system interacts with, and is a potent modulator of, the immune system. Endogenous catecholamine release caused by stress induces leucocytosis.[1–3] Exercise increases both lymphocyte and neutrophil numbers,[2 4] but major surgical stress causes lymphopenia with polymorphonuclear leucocytosis.[1 5] Furthermore, increased release of cortisol accompanying stress, such as in major surgery, also affects leucocyte numbers.[6 7] Exogenous administration of adrenaline also induces leucocytosis with an initial increase in lymphocytes followed by neutrophilia and relative lymphopenia.[7–9]

Lymphocytes can be divided further into several subsets which include B lymphocytes, T lymphocytes and natural killer (NK) cells. Exercise-induced increases in adrenaline result in lymphocytosis, with a three-fold increase in cytotoxic T cells ($CD8^+$) and NK cells, and a smaller increase in helper T cells ($CD4^+$).[10 11] Exogenous administration of adrenaline alters the subtypes of lymphocytes: an increase in NK cells has been found consistently,[6 7 12 13] but although Brohee and colleagues[7] showed an increase in all lymphocytic subtypes, others have found that total T cell ($CD3^+$) and $CD4^+$ counts decreased.[6 12 13] This effect is thought to be caused by stimulation of $\beta_2$-adrenergic receptors on lymphocytes.[10 14 15] Prolonged exposure to catecholamines can lead to a reduction in the number of circulating lymphocytes in healthy volunteers.[16]

Catecholamines also affect white cell function. Administration of adrenaline has been shown to decrease neutrophil adherence *in vitro*,[13 17] decrease chemotaxis[18] and enhance NK activity.[6 12 19] Such changes in the immune system may be clinically important after major surgery, trauma and in the critically ill patient with sepsis.

The majority of studies in this field have been performed with adrenaline as the primary stimulant. Adrenaline stimulates $\alpha_1$-, $\beta_1$- and $\beta_2$-adrenergic receptors. In contrast, the synthetic inotropic agents dobutamine and dopexamine have no $\alpha_1$ agonist

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activity. Dobutamine is a $\beta_1$- and $\beta_2$-adrenoceptor agonist,[20] while dopexamine stimulates dopaminergic and $\beta_2$- adrenoceptors, with minimal $\beta_1$-receptor activity.[21] Park, Couzens and Hoskins found that total white cell count increased during infusion of dopamine, dobutamine or dopexamine,[22] but little is known of the effects of these synthetic inotropic agents on white cell populations and function. The complexity of the interactions between the immune system and the neuroendocrine system make it unwise to extrapolate from studies with adrenaline to newer inotropic agents with different adrenergic receptor specificity. In view of the large number of immune variables thought to be affected by these agents, we chose to perform a pilot study. The aim of this study was to investigate the effects of inotropes with different adrenoceptor specificity on differential white cell count, lymphocyte subtypes and neutrophil function in six healthy volunteers.

## Subjects and methods

This pilot study was a placebo-controlled study of the effects of adrenaline, dobutamine and dopexamine on white cell count, lymphocyte subtype count and neutrophil function in healthy volunteers. Volunteers were studied on four different occasions, each at least 1 week apart. All studies started between 08:00 and 09:30 to avoid confounding effects of circadian rhythms on the variables measured. Each volunteer was allocated randomly to receive the different agents in a different order. Volunteers and laboratory investigators, but not the clinical investigator, were blinded to the drug administered. Approval from the local District Ethics Committee was obtained.

We studied six healthy male volunteers. Before recruitment, any volunteer with a history of chronic illness, receiving treatment for intercurrent illness, a history of drug or alcohol (>25 units/week) abuse or cigarette smoking, or known allergy to inotropic agents was excluded. Written informed consent was obtained from each volunteer and a full physical examination with laboratory and electrocardiographic assessment was performed by an independent physician, before and at the end of the study.

### INOTROPE ADMINISTRATION

The study was conducted in an area which had full resuscitation facilities and a physician in attendance at all times. A 16-gauge cannula was inserted into each forearm under local anaesthesia: one cannula was used for blood sampling and the other for administration of the test substance only. Haemodynamic monitoring with continuous ECG and an automatic intermittent arterial pressure monitoring device was then started. After a baseline reading, arterial pressure was measured at 2 and 5 min after starting the infusion, and then at 5-min intervals throughout the infusion and the 30-min period after the infusion was stopped. Additional readings were obtained at 3 and 4 h after starting the study. Volunteers remained recumbent throughout the study. Coffee or tea was avoided for 8 h before the study, and only orange squash, toast and biscuits were allowed throughout the study.

Volunteers were studied during a 2-h infusion, and for 2 h after completion of the study. The agents investigated were adrenaline 0.1 $\mu g\ kg^{-1}\ min^{-1}$, dobutamine 5 $\mu g\ kg^{-1}\ min^{-1}$, dopexamine 2 $\mu g\ kg^{-1}\ min^{-1}$ and 5% glucose 0.5 $ml\ kg^{-1}\ h^{-1}$ as placebo. The infusion rate was halved or stopped if heart rate exceeded 120 beat $min^{-1}$, arrhythmia developed or mean arterial pressure changed by more than 20 mm Hg.

Venous blood was sampled before starting the infusion ($t$=0), at 30 and 120 min after starting the infusion, and 2 h after stopping the infusion. A maximum of 30 ml of blood were required at each sampling time: 20 ml of heparinized blood for neutrophil studies, 2×2.7 ml in EDTA for differential white cell count and lymphocyte subtypes, and 5 ml of spare serum in the event of further tests being required to validate results. Differential white count and lymphocyte subtypes were measured at all four times, and neutrophil function was measured at 0, 30 and 120 min.

### MEASUREMENT OF HAEMATOLOGICAL AND IMMUNOLOGICAL VARIABLES

A full blood count and white cell differential count were performed using a STK-S Coulter counter (Coulter Electronics, UK). Where an automated white cell differential count could not be obtained, a manual white cell differential was performed.

Lymphocyte subtypes were assessed by dual colour immunofluorescence using a lysed whole blood technique. The markers used were $CD19^+$ (B cells), $CD3^+$ (total T cells), $CD4^+$ (T helper cells), $CD8^+$ (cytotoxic T cells), $CD3^+$/DR co-expression (activated T cells) and $CD16^+$ (NK cells). All reagents were from the Simulset range of monoclonal antibodies (Becton Dickinson, Oxford, UK). The percentage of each T cell subtype was measured by flow cytometry using a FACScan (Becton Dickinson, Oxford, UK) and Simulset software. Absolute values were calculated from this percentage and lymphocyte count from full blood count.

Blood for neutrophil function assays was obtained under pyrogen-free conditions into preservative-free heparin. All assays of neutrophil function were carried out under pyrogen-free conditions. The assays used do not require highly purified neutrophil populations, and so gravity sedimented leucocytes were used to avoid unnecessary manipulation of neutrophils.

Neutrophil respiratory burst in response to formyl-methionyl-leucyl-phenylalanine (fMLP) (Sigma, UK) was assessed using a luminol-enhanced chemoluminescence system. Phagocytosis of both opsonized and unopsonized zymosan was assessed indirectly, using a luminol-enhanced chemoluminescence system. The chemotactic response (directional movement of neutrophils towards a stimulus with chemoattractant properties) together with chemokinesis (non-directional, random neutrophil motility) was assessed under agarose.[23] The chemotactic responses to different stimuli (fMLP, autologous serum, zymosan-activated serum and normal pooled human serum) were tested. Neutrophil adhesion to protein-coated glass was assessed by microscopy in a chamber assay.[24] The expression of CD11b, a component of the CD11b/CD18 integrin adhesion molecule, was measured by flow cytometry.

### STATISTICAL ANALYSIS

As all of the immunological variables measured vary greatly both within- and between-individuals, changes during each study were expressed as percentage change from baseline (measurement at $t=0$). Results are expressed as mean (SEM) percentage change from baseline where $n=6$. The Wilcoxon signed rank test was used to compare differences between placebo and active drugs on changes from baseline at each time.

## Results

All six volunteers completed the four study periods. The infusion rate was halved only once, when mean arterial pressure decreased by greater than 20%, 5 min after an infusion of adrenaline was started. Arterial pressure then returned to baseline values. On all other occasions heart rate and mean arterial pressure remained within the predetermined limits. No arrhythmias occurred. Volunteers noted a variety of subjective sensations, including tremor, headache and awareness of the heart beating, but they were not distressed by these symptoms.

Data for all variables were obtained, except in the following instances: monocyte and basophil counts were not obtained for one study because of a technical problem with the Coulter counter, and platelet count was not obtained for all four studies in one volunteer because of platelet clumping. This is a problem which can occur in normal individuals and did not signify any significant underlying disease.

### HAEMATOLOGICAL VARIABLES

Mean percentage changes from baseline for differential white cell count and lymphocyte subtypes that occurred during infusion of each of the four agents at each time, and the significance of these changes compared with placebo, are shown in tables 1 and 2, respectively. Infusion of adrenaline was associated with significant leucocytosis, lymphocytosis and neutrophilia, whereas infusions of dobutamine and dopexamine were associated with a significant decrease in white cell, lymphocyte and neutrophil counts. These changes were also apparent for absolute CD3$^+$ count (total T cells), absolute CD4$^+$ count (helper T cells) and absolute CD8$^+$ count (cytotoxic T cells). Monocytes increased significantly only during infusion of adrenaline, whereas eosinophil count increased initially with infusion of adrenaline, and then decreased with infusion of all three agents. There were no significant changes in haemoglobin, packed cell volume or red cell count. Platelet count increased significantly with infusion of adrenaline compared with placebo at 30 ($P=0.043$) and 120 min ($P=0.043$).

### NEUTROPHIL FUNCTION

Mean percentage changes from baseline for the neutrophil function tests that occurred with infusion of each of the four agents at each time, and the significance of these changes compared with placebo, are shown in table 3. There was a significant increase in chemoluminescence with infusion of adrenaline for 30 min compared with placebo ($P=0.046$). Neutrophil adhesion, CD11b expression and phagocytosis were not changed significantly by infusion of any of the test drugs at the given dose. Chemotaxis (directional neutrophil movement) to fMLP, the volunteer's own serum, normal human serum and zymosan-activated serum did not change significantly. Chemokinesis (non-directional random

*Table 1* Mean (SEM) percentage changes from baseline in differential white cell count at 30, 120 and 240 min after starting the four infusions ($n=6$). *$P<0.05$ (Wilcoxon signed rank test)

| | Total white cell count | | | Lymphocyte count | | | Neutrophil count | | |
|---|---|---|---|---|---|---|---|---|---|
| Time (min) | 30 | 120 | 240 | 30 | 120 | 240 | 30 | 120 | 240 |
| Glucose | −1.67<br>(4.4) | +6.92<br>(4.7) | +10.5<br>(5.1) | −2.8<br>(8.2) | +5.8<br>(11.9) | +13.7<br>(6.4) | −0.13<br>(3.2) | +10.3<br>(5.4) | +7.67<br>(12.6) |
| Adrenaline | +70.5<br>(12.8)* | +60.1<br>(13.4)* | +91.8*<br>(29.2)* | +126<br>(28.7)* | +37.1<br>(12.2)* | −5.0<br>(6.6)* | +33.6<br>(6.2)* | +82.0<br>(21.7)* | +160<br>(48.2)* |
| Dobutamine | −8.3<br>(2.0) | −11.2<br>(2.8)* | −1.7<br>(2.9) | −6.4<br>(3.4) | −16.2<br>(6.8)* | −4.2<br>(3.6) | −9.8<br>(2.0)* | −8.2<br>(4.1)* | −3.1<br>(3.9) |
| Dopexamine | −6.3<br>(2.3) | −13.5<br>(2.6)* | +1.5<br>(5.6) | +14.4<br>(10.5)* | −11.9<br>(8.2)* | −16.1<br>(7.8)* | −15.1<br>(1.8)* | −11.2<br>(3.4)* | +11.4<br>(12.9) |

| | Monocyte count | | | Basophil count | | | Eosinophil count | | |
|---|---|---|---|---|---|---|---|---|---|
| Time (min) | 30 | 120 | 240 | 30 | 120 | 240 | 30 | 120 | 240 |
| Glucose | −4.7<br>(4.4) | −13.0<br>(6.8) | +1.8<br>(8.3) | +12.5<br>(20.4) | 0<br>(16.1) | +147.5<br>(153) | −8.1<br>(4.2) | +4.4<br>(7.7) | +5.0<br>(2.7) |
| Adrenaline | +81.6<br>(19.2)* | +56.8<br>(11.2)* | +106<br>(49.5) | +38.5<br>(37.1) | −61.5<br>(21.6) | −46.2<br>(38.2) | +54.9<br>(12.1)* | −18.1<br>(8.1) | −51.9<br>(6.5)* |
| Dobutamine | −12.9<br>(6.8) | −15.2<br>(5.1) | −6.8<br>(5.0) | −39.3<br>(15.3) | −10.7<br>(53.7) | 71.4<br>(185) | −17.9<br>(5.9) | −29.3<br>(2.8)* | −28.6<br>(7.6)* |
| Dopexamine | −21.0<br>(5.6) | −21.0<br>(7.0) | +3.6<br>(15.4) | +44.4<br>(56.2) | −27.8<br>(14.2) | 350<br>(196) | −42.6<br>(7.4)* | −54.1<br>(3.9)* | −61.5<br>(4.5)* |

*Table 2* Mean (SEM) percentage changes from baseline in lymphocyte subsets at 30, 120 and 240 min after starting the four infusions ($n=6$). *$P<0.05$ (Wilcoxon signed rank test)

| | CD19 absolute count (B cells) | | | CD3 absolute count (total T cells) | | | ACT absolute count (activated T cells) | | |
|---|---|---|---|---|---|---|---|---|---|
| Time (min) | 30 | 120 | 240 | 30 | 120 | 240 | 30 | 120 | 240 |
| Glucose | +1.5<br>(9.9) | +13.2<br>(14.8) | +11.2<br>(13.1) | −2.1<br>(7.2) | +7.7<br>(10.8) | +14.9<br>(7.1) | −5.6<br>(5.5) | +23.1<br>(16.9) | +36.1<br>(13.7) |
| Adrenaline | +50.3<br>(49.9) | +16.0<br>(9.4) | +15.4<br>(21.5) | +96.5<br>(19.8)* | +23.3<br>(10.6) | −10.6<br>(7.9) | +263<br>(135)* | +70.8<br>(24.3) | −29.2<br>(13.7) |
| Dobutamine | −20.0<br>(4.2) | −6.1<br>(9.4) | +9.4<br>(6.0) | −13.1<br>(3.2)* | −19.0<br>(7.5)* | −5.2<br>(5.2) | +13.9<br>(14.8) | −11.8<br>(11.2) | −21.6<br>(5 7)* |
| Dopexamine | −22.1<br>(5.0) | −23.6<br>(5.6) | −18.1<br>(14.7) | +1.1<br>(8.9) | −19.1<br>(7.0)* | −15.9<br>(9.2) | +20.6<br>(9.0) | −21.6<br>(12.4) | −28.4<br>(15.3)* |

| | CD4 absolute count (T helper cells) | | | CD8 absolute count (T suppressor cells) | | | NK absolute count (natural killer cells) | | |
|---|---|---|---|---|---|---|---|---|---|
| Time (min) | 30 | 120 | 240 | 30 | 120 | 240 | 30 | 120 | 240 |
| Glucose | −3.6<br>(6.8) | +7.1<br>(10.1) | +15.2<br>(5.8) | −3.1<br>(9.3) | +9.4<br>(15.4) | +19.7<br>(8.6) | 0<br>(22.9) | +32<br>(35 3) | +74<br>(35.1) |
| Adrenaline | +69.9<br>(22.4)* | +1.5<br>(10.4) | 0<br>(7.1) | +213<br>(32.3)* | +53<br>(20.3) | +130<br>(136)* | +739<br>(345)* | +340<br>(106) | +1.3<br>(17.1)* |
| Dobutamine | −12.5<br>(2.2) | −17.6<br>(6.7)* | +2.7<br>(4.1) | +15.0<br>(7.3) | −9.8<br>(7.5) | −6.8<br>(4.5)* | +69<br>(36.6) | −6.3<br>(12.5) | −25<br>(12 9)* |
| Dopexamine | −29.9<br>(13.8) | −19.1<br>(5.7)* | −8.2<br>(10.2) | +40.0<br>(17.9)* | −5.6<br>(11.6) | −31.0<br>(5.4)* | +216<br>(80.9)* | +75<br>(42.0) | +35<br>(50.8) |

*Table 3* Mean (SEM) percentage changes from baseline in neutrophil function tests at 30 and 120 min after starting the four infusions ($n=6$). *$P<0.05$ (Wilcoxon signed rank test)

| | Chemoluminescence | | Phagocytosis (opsonized zymosan) | | Adhesion | | Chemotaxis to fLMP | |
|---|---|---|---|---|---|---|---|---|
| Time (min) | 30 | 120 | 30 | 120 | 30 | 120 | 30 | 120 |
| Glucose | +3.0<br>(36.8) | −9.1<br>(26.4) | −19.2<br>(15.3) | −0.8<br>(25.7) | −20.1<br>(15.7) | −26.2<br>(8.5) | +18.5<br>(18.7) | +13.9<br>(13.9) |
| Adrenaline | +55.8<br>(19.4)* | +23.8<br>(20.5) | +12.9<br>(25.0) | +29.0<br>(19.3) | +1.3<br>(16.9) | −16.1<br>(13.5) | +27.2<br>(19.9) | +17.7<br>(12.4) |
| Dobutamine | −20.7<br>(439) | −27.8<br>(180) | +14.7<br>(29.2) | +6.4<br>(32.8) | −32.3<br>(6.9) | −19.4<br>(8.2) | +18.0<br>(15.7) | +11.3<br>(10.4) |
| Dopexamine | +32.1<br>(65.1) | +16.5<br>(64.6) | −29.8<br>(16.9) | +13.7<br>(41.3) | −31.9<br>(7.7) | −34.1<br>(12.4) | −4.2<br>(10.5) | −5.2<br>(2.4) |

| | Chemotaxis to autologous serum | | Chemotaxis to zymosan activated serum | | Chemotaxis to normal pooled serum | | Chemokinesis | |
|---|---|---|---|---|---|---|---|---|
| Time (min) | 30 | 120 | 30 | 120 | 30 | 120 | 30 | 120 |
| Dextrose | +7.0<br>(33.6) | +19.9<br>(16.0) | +32.3<br>(41.9) | +12.1<br>(17.9) | −0.2<br>(35.8) | +18.3<br>(16.1) | −8.3<br>(12.6) | +5.8<br>(15.8) |
| Adrenaline | +59.9<br>(26.6) | +38.0<br>(20.1) | +28.6<br>(14.6) | +37.1<br>(26.2) | +23.2<br>(12.8) | +29.6<br>(32.1) | −20.0<br>(12.4) | −12 9<br>(23.3) |
| Dobutamine | +36.3<br>(23.3) | +51.3<br>(26.4) | +72.7<br>(23.7) | +54.9<br>(15.7) | +62.5<br>(37.3) | +72.6<br>(29.8) | +35.1<br>(26.8)* | +48.9<br>(19.6) |
| Dopexamine | −7.2<br>(15.0) | +71.8<br>(24.1) | −10.4<br>(23.0) | +61.3<br>(52.6) | −21.2<br>(8.6) | +45.0<br>(37.3) | +12.9<br>(16.8) | +70.5<br>(22.2) |

movement) increased significantly 30 min after infusion of dobutamine compared with placebo ($P=0.03$). However, as chemotaxis was unaffected, this effect is unlikely to be clinically relevant.

## Discussion

We found a significant increase in white cell count, lymphocyte count and neutrophil count with adrenaline, and a small but significant decrease in these variables with dobutamine and dopexamine. These trends were also apparent for absolute CD3$^+$, CD4$^+$ and CD8$^+$ counts. Chemoluminescence increased significantly only with adrenaline, and there were no other significant changes in tests of neutrophil function.

Leucocytosis, lymphocytosis and neutrophilia in association with exogenous administration of adrenaline is well recognized. Changes in circulating leucocyte numbers may be caused by an absolute change in total leucocyte count or alteration in the fraction of leucocytes present in the circulation. Two populations of neutrophils have been identified: circulating and marginal. Adrenaline appears to mobilize the marginating pool into the circulating pool without altering the total neutrophil population.[25] After major surgical stress lymphopenia is associated with redistribution of lymphocytes from the blood to lymphatic tissue.[26] Of interest was the significant decrease in white cell numbers, lymphocyte and neutrophil counts which was evident during infusion of the synthetic agents dobutamine and dopexamine. These trends were also apparent for absolute $CD3^+$ count (total T cells), absolute $CD4^+$ count (helper T cells) and absolute $CD8^+$ count (cytotoxic T cells). All three agents increased natural killer cell count, as has been described previously with adrenaline. These changes are of interest, but are difficult to interpret in a clinical setting as they probably reflect transient changes in the intravascular pool which may not reflect events in the tissues. Our results are in contrast with the increase in white cell count seen with infusion of dobutamine or dopexamine in the study by Park, Couzens and Hoskins,[22] which may reflect the higher doses of these agents used in their study. The differences between adrenaline and the synthetic inotropes may reflect the different $\beta_2$-adrenergic activity of the agents, despite the doses being chosen with a view to equipotency. However, each volunteer has a different pharmacodynamic response to each agent, depending on factors such as the concentration of endogenous circulating catecholamines, and variation between individuals for a given dose may account in part for the differences seen.

The numbers of monocytes increased only during infusion of adrenaline, whereas eosinophil count increased initially with infusion of adrenaline, and then decreased with infusion of all three agents. These changes probably reflect changes in the white cell populations between circulating and marginal pools. A significant increase in platelet count was seen only with adrenaline. Adrenergic stimulation increases platelet numbers and activation, while $\beta_2$-adrenergic stimulation decreases platelet numbers and platelet aggregation.[27 28] The effect of adrenaline was caused presumably by $\alpha$-adrenergic stimulation; neither dobutamine nor dopexamine possess $\alpha$-agonist activity. It is important that clinicians recognize such effects when interpreting laboratory data from patients receiving these agents, as this may avoid unnecessary investigation of drug-related changes.

The effect of infusion of adrenaline on chemoluminescence is of interest, suggesting an increase in the generation of reactive oxygen species by the neutrophil. However, another possible explanation is that the marginating neutrophil pool mobilized by adrenaline may be of a functionally more active group of neutrophils. The role of neutrophil activation resulting in increased free radical production and direct tissue damage in the pathophysiology of multiple organ failure and acute lung injury is well recognized.[29 30] In view of the widespread use of inotropes, the relevance of neutrophil activation in patients would certainly be worthy of further study. As adrenaline, dobutamine and dopexamine infusions had no effect on neutrophil chemotaxis, it is unlikely that the acute effect of dobutamine on chemokinesis is clinically important.

This preliminary study was designed to identify specific variables which could then be studied on a larger scale in both volunteers and specific patient populations. The problems associated with determining a normal range for lymphocyte subsets and neutrophil function are reduced by using volunteers as their own controls. While a small study in which so many variables are measured is likely to show some statistically significant results, further work is required to determine which of these results is clinically important.

In summary, this study suggests that infusion of inotropes was associated with changes in white cell numbers, lymphocyte subsets and neutrophil respiratory burst. Adrenaline had effects different from those of the synthetic inotropic agents, dobutamine and dopexamine, at least in healthy volunteers. The study highlighted areas in which further work is needed to determine the clinical relevance of immunological effects of different inotropic agents.

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# Can prolonged expiration manoeuvres improve the prediction of arterial $P\text{CO}_2$ from end-tidal $P\text{CO}_2$?

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## Summary

We have studied, in 16 patients undergoing thoracoabdominal oesophagectomy, if two prolonged expiration manoeuvres improve prediction of arterial $P\text{CO}_2$ ($Pa_{\text{CO}_2}$) from end-tidal $P\text{CO}_2$ ($P\text{E}'_{\text{CO}_2}$). $P\text{E}'_{\text{CO}_2}$, $P\text{CO}_2$ at the end of a simple prolonged expiration ($P\text{E}_{1\,\text{CO}_2}$), and $P\text{CO}_2$ at the end of a prolonged expiration preceded by sustained hyperinflation of the lungs ($P\text{E}_{2\,\text{CO}_2}$), were measured during laparotomy, in the lateral thoracotomy position during two-lung ventilation, and after transition to one-lung ventilation. ($Pa_{\text{CO}_2}-P\text{E}'_{\text{CO}_2}$) was 1.3 (SD 0.4) kPa during laparotomy and this remained stable throughout the study. Both manoeuvres decreased the mean arterial to peak expired $P\text{CO}_2$ difference, particularly during one-lung ventilation. However, $P\text{E}_{1\,\text{CO}_2}$ and $P\text{E}_{2\,\text{CO}_2}$ did not agree more closely with $Pa_{\text{CO}_2}$ than $P\text{E}'_{\text{CO}_2}$ at any stage of the study. We conclude that these manoeuvres did not improve estimation of $Pa_{\text{CO}_2}$ from $P\text{E}'_{\text{CO}_2}$. (*Br. J. Anaesth.* 1997; **78**: 536–540).

**Key words**
Carbon dioxide, partial pressure. Carbon dioxide, measurement. Partial pressure, end-tidal. Partial pressure, arterial. Partial pressure, carbon dioxide. Surgery, thoracic. Surgery, abdominal. Monitoring, carbon dioxide.

Continuous measurement of end-tidal carbon dioxide partial pressure ($P\text{E}'_{\text{CO}_2}$) has long been used for non-invasive estimation of arterial $P\text{CO}_2$ ($Pa_{\text{CO}_2}$) during anaesthesia.[1,2] However, a major concern is that $P\text{E}'_{\text{CO}_2}$ generally underestimates $Pa_{\text{CO}_2}$, with variations both between and within subjects.[3–5] The arterial to end-tidal $P\text{CO}_2$ difference ($Pa_{\text{CO}_2}-P\text{E}'_{\text{CO}_2}$) depends on the spread of ventilation–perfusion ratios. One index of an increased spread of ventilation–perfusion ratios is an increased slope of the "expiratory plateau" of the single breath test (expired carbon dioxide plotted against expired volume).[6] Thus individuals with an increased phase III slope on the capnogram often have an increased arterial to end-tidal $P\text{CO}_2$ difference.[4] During controlled ventilation in adults, the "expiratory plateau" is usually flat and nearly horizontal, but several factors, such as age and airways disease, and in particular smoking, are associated with an increase in the slope of the "expiratory plateau".[5,6] In this situation, the $P\text{E}'_{\text{CO}_2}$ value cannot be taken as a good estimate of alveolar $P\text{CO}_2$ and hence not as an estimate of $Pa_{\text{CO}_2}$. In this case, a simple prolonged expiration (permitting expiration to continue for 5–15 s) or a forced expiration (induced by a gentle squeeze on the patient's chest) may give a more representative estimation of $Pa_{\text{CO}_2}$.[7,8] Thus these manoeuvres are currently recommended to improve prediction of $Pa_{\text{CO}_2}$ from $P\text{E}'_{\text{CO}_2}$, especially when a steeply sloping "plateau" is observed.[9,10] However, the validity and usefulness of these measurements in individual patients have not been investigated.

Patients with oesophageal carcinoma are almost exclusively smokers with resultant airways disease. Their ($Pa_{\text{CO}_2}-P\text{E}'_{\text{CO}_2}$) and the phase III slope of their capnogram would thus be expected to be increased during anaesthesia, especially during thoracotomy.[11,12] We have therefore studied in patients undergoing thoracoabdominal oesophagectomy two prolonged expiration manoeuvres in order to assess if this improves prediction of $Pa_{\text{CO}_2}$ from $P\text{E}'_{\text{CO}_2}$.

## Patients and methods

We studied 16 successive patients (14 males), mean age 60 (range 48–71) yr, undergoing thoracoabdominal oesophagectomy for cancer. All patients were devoid of symptomatic cardiac disease. Fourteen were smokers. Lung function tests ($\text{FEV}_1$, FVC) were performed before operation. The study was approved by the Ethics Committee of our University Hospital and all patients gave informed consent.

Patients were premedicated with hydroxyzine 100 mg orally, 90 min before induction of anaesthesia with fentanyl 5 $\mu$g kg$^{-1}$ and thiopentone 5 mg kg$^{-1}$. Pancuronium 0.1 mg kg$^{-1}$ was administered to produce neuromuscular block and facilitate tracheal intubation. Anaesthesia was maintained with fentanyl, and enflurane with 50% nitrous oxide in oxygen. Anaesthetic agents were administered as required to avoid variations in mean arterial pressure

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>20% of baseline. Intraoperative monitoring consisted of continuous electrocardiography, pulse oximetry, direct arterial pressure measurement via a radial artery cannula and rectal temperature. For the abdominal procedure, the lungs were ventilated mechanically (Monnal D2 ventilator) at a ventilatory frequency of 12 bpm with a tidal volume of 10–12 ml $kg^{-1}$ and an inspiratory:expiratory (I:E) ratio of 1:2. After abdominal wound closure, a double-lumen endobronchial tube with a left-sided bronchial stem (Carlens tube) was sited for right thoracotomy. Endobronchial tube position and isolation of the two lumens were checked by auscultation, spirometry and respiratory gas detection with the patient in the lateral position. During one-lung ventilation (OLV), ventilatory settings were ventilatory frequency 15 bpm, tidal volume 8 ml $kg^{-1}$ and I:E ratio 1:2.

### PROLONGED EXPIRATION MANOEUVRES

To obtain a prolonged expiration, the ventilator was abruptly set, during one expiration, to spontaneous ventilation to permit expiration to continue for 10–20 s. Maximum concentration of expired carbon dioxide ($FE_1\ CO_2$) was then recorded. Values were considered valid when a well identified "plateau" was obtained. For the second manoeuvre, a 3-litre reservoir bag connected to the ventilator system was used. Lungs were inflated manually with fresh gases (oxygen and nitrous oxide) contained in the bag until airway pressure reached 35 cm $H_2O$. This pressure was held for 3 s, and then full expiration was permitted, with recording of maximum concentration of expired carbon dioxide ($FE_2\ CO_2$). Manoeuvres were performed in this non-randomized order because, in preliminary measurements, $FE_1\ CO_2$ increased when recorded immediately after $FE_2\ CO_2$.

### MEASUREMENTS

$Pa_{CO_2}$ was measured at 37 °C in duplicate (ABL 500 and 510, Radiometer), and values were corrected to the patient's temperature according to the following formula[13]:

$$Pa_{CO_2}=Pa_{CO_2}\,(37\,°C)-10^{0.019\,(T°-37)},$$

where $T°$=patient temperature. The differences between arterial and expired carbon dioxide partial pressures were calculated using temperature-corrected $Pa_{CO_2}$ values. End-tidal carbon dioxide fractions ($FE'_{CO_2}$, $FE_1\ CO_2$ and $FE_2\ CO_2$) were measured from gas sampled between the tracheal (or endobronchial) tube and the Y-piece of the ventilator tubing using a sidestream infrared capnometer (Capnomac Ultima, Datex) calibrated according to the manufacturer's instructions before use in each patient.[14] The capnograph traces were recorded (7041 M X-Y recorder, Hewlett-Packard) for analysis of the slope of the phase III of the capnograms. The "alveolar plateau" was arbitrarily considered normal (i.e. nearly horizontal) when the trace virtually did not increase in the final portion (last third) of the phase III of the capnogram. $PE'_{CO_2}$, $PE_1\ CO_2$ and $PE_2\ CO_2$ were obtained from $FE'_{CO_2}$, $FE_1\ CO_2$ and $FE_2\ CO_2$, respectively, according to the formula:

$$PCO_2=FCO_2-(Pb-PH_2O)$$

where Pb=barometric pressure and $PH_2O$=water vapour pressure at 37 °C. At each stage of the study, mean arterial pressure, heart rate and rectal temperature were measured. Blood was then sampled from the radial artery cannula for immediate $Pa_{CO_2}$ measurement. Syringes were rinsed with sodium heparin to prevent coagulation. Simultaneously, $FE'_{CO_2}$ was recorded. Then, $FE_1\ CO_2$ and $FE_2\ CO_2$ were obtained successively by appropriate manoeuvres. Finally, arterial blood was sampled for $Pa_{CO_2}$ measurement to verify stability of $Pa_{CO_2}$ during the procedure. The time necessary to obtain the entire set of measurements was <10 min.

Initial measurements were made during the abdominal procedure, before wound closure (T1). A second set of measurements was performed with the patient in the lateral position after 20 min with two-lung ventilation (TLV) (T2). After transition to OLV with the pleura open, measurements were repeated after an additional 20 min (T3) and 50 min (T4). A final set of measurements was obtained after wound closure, after 20 min with TLV, with the patient in the lateral position (T5).

### STATISTICAL ANALYSIS

Values of the differences between $Pa_{CO_2}$ and each end-expiratory carbon dioxide partial pressure (i.e. ($Pa_{CO_2}-PE'_{CO_2}$), ($Pa_{CO_2}-PE_1\ CO_2$) and ($Pa_{CO_2}-PE_2\ CO_2$)) were computed at each sample point, with results expressed as mean (SD). Differences were analysed using two-way analysis of variance for repeated measurements. Multiple comparisons were made with Fisher's protected least significant difference testing. $P<0.05$ was considered significant. To assess the usefulness of each prolonged expiration manoeuvre to improve estimates of $Pa_{CO_2}$ from end-expiratory $PCO_2$, mean values for arterial to end-expiratory $PCO_2$ differences were used as the mean error (or bias) of the method tested (i.e. $PE'_{CO_2}$, $PE_1\ CO_2$ and $PE_2\ CO_2$) relative to $Pa_{CO_2}$. The SD of the differences were used as the precision of the method tested. The mean range difference (2 SD) defined the 95% limits of agreement of each end-expiratory measure *vs* $Pa_{CO_2}$.[15]

## Results

Lung function tests ($FEV_1$, FVC) were not performed in two asymptomatic non-smoking patients.

*Table 1* Preoperative spirometry data in 14 patients

| Patient No. | $FEV_1$ (% expected) | FVC (% expected) |
|---|---|---|
| 1 | 85 | 80 |
| 2 | 100 | 110 |
| 3 | 75 | 75 |
| 4 | 50 | 84 |
| 5 | 85 | 100 |
| 6 | 80 | 85 |
| 7 | 85 | 90 |
| 8 | 113 | 110 |
| 9 | 125 | 112 |
| 10 | 90 | 85 |
| 11 | 80 | 80 |
| 12 | 75 | 100 |
| 13 | 70 | 75 |
| 14 | 110 | 100 |

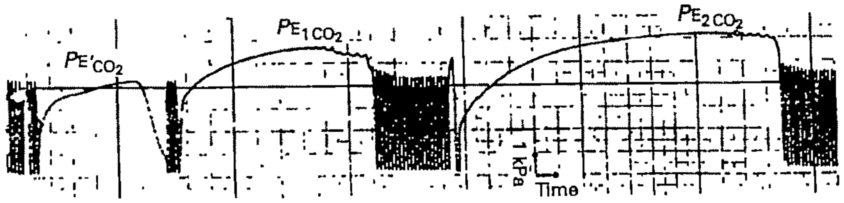

*Figure 1* Typical example of $PE'_{CO_2}$ (end-tidal carbon dioxide partial pressure), $PE_1$ $_{CO_2}$ (peak expired carbon dioxide partial pressure during prolonged expiration) and $PE_2$ $_{CO_2}$ (peak expired carbon dioxide partial pressure during prolonged expiration after manual hyperinflation) measurements, showing capnographic recordings during one-lung ventilation. A steep phase III slope without a good plateau was observed in the capnogram, and prolonged expiration manoeuvres clearly increased peak expired carbon dioxide partial pressure (with $PE_2$ $_{CO_2}$>$PE_1$ $_{CO_2}$).

*Table 2* $Pa_{CO_2}$ and arterial to peak expired partial pressure differences in 16 patients undergoing thoracoabdominal oesophagectomy (mean (SD)). $PE_1$ $_{CO_2}$=peak expired carbon dioxide partial pressure during prolonged expiration; $PE_2$ $_{CO_2}$=peak expired carbon dioxide partial pressure during prolonged expiration following manual hyperinflation. Significant differences: *$P$<0.01 *vs* ($Pa_{CO_2}$−$PE'_{CO_2}$); †$P$<0.01 *vs* ($Pa_{CO_2}$−$PE_1$ $_{CO_2}$); ‡$P$<0.01 *vs* T2

| Measurement | $Pa_{CO_2}$ (kPa) | $Pa_{CO_2}$−$PE'_{CO_2}$ (kPa) | $Pa_{CO_2}$−$PE_1$ $_{CO_2}$ (kPa) | $Pa_{CO_2}$−$PE_2$ $_{CO_2}$ (kPa) |
|---|---|---|---|---|
| T1 (end of abdominal procedure) | 5.3 (0.6) | 1.3 (0.4) | 0.8 (0.5)* | 0.6 (0.5)*† |
| T2 (TLV for 20 min) | 5.3 (0.6) | 1.4 (0.5) | 1.0 (0.6)* | 0.4 (0.6)*† |
| T3 (OLV for 20 min) | 5.5 (0.6) | 1.3 (0.4) | 0.4 (0.5)*‡ | −0.1 (0.5)*†‡ |
| T4 (OLV for 50 min) | 5.5 (0.6) | 1.4 (0.5) | 0.3 (0.6)*‡ | −0.2 (0.5)*†‡ |
| T5 (TLV, after skin closure) | 5.3 (0.6) | 1.2 (0.5) | 0.5 (0.7)*‡ | 0.1 (0.6)*†‡ |

Preoperative spirometry results were <80% of expected values in four of 14 patients (table 1). $Pa_{CO_2}$ was almost unchanged during each stage of the study in all patients (the larger variation observed in one set of measurements was 0.5 kPa). For analysis, $Pa_{CO_2}$ values before and after each set of measurements were averaged. Heart rate and mean arterial pressure were maintained within 20% of baseline when measurements were performed, and moderate progressive hypothermia was observed (from 37.2 (SD 0.3) °C at T1 to 36.2 (0.4) °C at T5).

Typical examples of capnographic traces obtained with both manoeuvres are shown in figure 1. At T1, $Pa_{CO_2}$ was 5.3 (0.6) kPa and $PE'_{CO_2}$ was 4.0 (0.5) kPa, and both remained unchanged throughout the study. As a result, ($Pa_{CO_2}$−$PE'_{CO_2}$), observed at T1, was 1.3 (0.4) kPa, and did not change significantly at each stage of the study (table 2). However, analysis of the capnograms showed that an almost horizontal phase III was obtained in 13 patients at T1, and in only eight patients at T2. Moreover, all patients had steep phase III slopes without a good plateau at T3 and T4 (and 13 patients at T5).

Both prolonged expiration manoeuvres decreased markedly the mean arterial to peak expired carbon dioxide partial pressure difference throughout the study, particularly during OLV: ($Pa_{CO_2}$−$PE_1$ $_{CO_2}$) and ($Pa_{CO_2}$−$PE_2$ $_{CO_2}$) were significantly smaller than ($Pa_{CO_2}$−$PE'_{CO_2}$) at T1 (0.8 (0.5) kPa and 0.6 (0.5) kPa, respectively, $P$<0.01 *vs* $PE'_{CO_2}$) and decreased further after transition to OLV (table 2). In addition, ($Pa_{CO_2}$−$PE_2$ $_{CO_2}$) was significantly smaller than ($Pa_{CO_2}$−$PE_1$ $_{CO_2}$) at each stage of the study (table 2); T3, T4 and T5 values were not significantly different from zero.

However, the manoeuvres did not reduce the variations in ($Pa_{CO_2}$−$PE'_{CO_2}$) observed between patients. The agreement between each end-expiratory $P$CO$_2$ and $Pa_{CO_2}$, as represented by the SD of the differences, was not improved with $PE_1$ $_{CO_2}$ or $PE_2$ $_{CO_2}$ compared with $PE'_{CO_2}$ at any stage of the study (table 2). To quantify the size of the measurement error that could be observed in clinical practice, data from all stages of the study were pooled. The 95% limits of agreement of $PE_1$ $_{CO_2}$ and $PE_2$ $_{CO_2}$ compared with $Pa_{CO_2}$ were −0.6 to 1.8 kPa and −1.0 to 1.4 kPa, respectively (and 0.5–2.1 kPa for ($Pa_{CO_2}$−$PE'_{CO_2}$)). This represented a range of values larger than 25% of the estimated value ($Pa_{CO_2}$) and thus were considered clinically unacceptable.

The two manoeuvres did not reduce the variations observed within patients. To illustrate this phenomenon, differences between the largest and smallest gradients obtained throughout the study were calculated patient by patient for the three end-expiratory carbon dioxide partial pressures. The results ranged from 0.3 to 1.0 kPa (mean 0.5 (SD 0.2) kPa), 0.3 to 2.0 kPa (1.0 (0.6) kPa) and from 0.5 to 1.8 kPa (1.0 (0.5) kPa) for ($Pa_{CO_2}$−$PE'_{CO_2}$), ($Pa_{CO_2}$−$PE_1$ $_{CO_2}$) and ($Pa_{CO_2}$−$PE_2$ $_{CO_2}$), respectively.

## Discussion

We undertook a study to see if two prolonged expiration manoeuvres improved estimation of $Pa_{CO_2}$ from $PE'_{CO_2}$ in patients undergoing oesophageal surgery, to achieve a wide range of ($Pa_{CO_2}$−$PE'_{CO_2}$) values with increased phase III slopes. None of the methods tested improved prediction of $Pa_{CO_2}$, even in situations which are currently recommended (i.e. a capnogram with a steeply sloping "alveolar plateau").

The ($Pa_{CO_2}$−$PE'_{CO_2}$) value is known to be increased in several situations.[1-5] In our study, the widened ($Pa_{CO_2}$−$PE'_{CO_2}$) observed at the end of the abdominal procedure was characterized by a flat and nearly horizontal plateau of the capnogram in 13 patients. This may suggest predominance of spatial ventilation–perfusion mismatching associated with a situation that does not influence pulmonary mechanical properties where well perfused and under perfused lung units empty simultaneously.[16] However, asynchronous emptying combined with increased ventilation–perfusion spread cannot be eliminated. Analysis of the phase III slope of the capnogram, contrary to the single breath test ($PCO_2$ plotted against expired volume), may not be a function of ventilation–perfusion spread. A horizontal plateau on the capnogram is likely to be a result of absence of expiratory gas flow at the sampling site of the carbon dioxide analyser.[16] As a result, a moderate decrease in mean ($Pa_{CO_2}-PE'_{CO_2}$) was obtained with the first prolonged expiration manoeuvre ($PE_1\ _{CO_2}$).

A steep phase III slope was observed at further stages of the study. Few studies have examined the slope of the phase III of the capnograms during thoracotomy. Our results suggest that an increased slope may be present frequently, particularly during OLV. This may be attributed to alterations in the spread of ventilation–perfusion ratios within the lungs related to prolonged anaesthesia,[17 18] increased vertical height of the lungs in the lateral decubitus position[19] and also OLV.[12 20] In addition, variations in the physiological deadspace fraction of tidal volume may occur during thoracic surgery, depending on many factors (especially variations in pulmonary arterial pressure[21]) which affect distribution of ventilation and perfusion within the lungs. Both within-units and between-units ventilation–perfusion mismatching may be improved by increasing tidal volume, at least if frequency is reduced at the same time.[4] The ventilatory settings used in this study were different from those in a previous study,[20] but the values of ($Pa_{CO_2}-PE'_{CO_2}$) were similar in both studies. The steep phase III slope and the dramatic decrease in mean ($Pa_{CO_2}-PE'_{CO_2}$) obtained with the simple prolonged expiration manoeuvre during thoracotomy, and particularly during OLV, strongly suggest the existence of delayed and asynchronous emptying, resulting in dynamic lung hyperinflation. Dynamic lung hyperinflation often occurs during OLV when a double-lumen endobronchial tube is used.[22] When exhalation is not complete, the areas with high ventilation–perfusion (and thus low $PCO_2$) are the most significant contributors to $PE'_{CO_2}$, inducing ($Pa_{CO_2}-PE'_{CO_2}$) to increase. The simple prolonged expiration manoeuvre ($PE_1\ _{CO_2}$) allows the low ventilation–perfusion, high $PCO_2$ areas to leave lungs and to make a more substantial contribution to end-expiratory $PCO_2$. If such a full expiration is preceded by sustained hyperinflation of the lungs ($PE_2\ _{CO_2}$ in this study), the extra ventilation is distributed preferentially to dependent, hypoventilated but well perfused lung regions.[23 24] The wash-out of areas with ventilation–perfusion ratios close to zero resulted in smaller, and frequently negative, ($Pa_{CO_2}-PE_2\ _{CO_2}$) gradients during OLV. In relatively healthy, non-pregnant adults, the incidence of negative ($Pa_{CO_2}-PE'_{CO_2}$) differences during controlled ventilation is 0–12% of patients,[5] but manual compression of the thorax (providing a "forced" $PE'_{CO_2}$) induces a decrease in ($Pa_{CO_2}-PE'_{CO_2}$) with a high incidence of negative gradients in patients with or without lung disease.[8] In addition, during OLV the dependent lung is small, thus each tidal breath is relatively effective in that it has a small functional residual capacity (FRC) to wash-out. This reduced FRC may have contributed to the negative differences during OLV.[5]

The manoeuvres did not reduce the variations observed with $PE'_{CO_2}$ both between and within patients. The intraoperative ($Pa_{CO_2}-PE'_{CO_2}$) relationship is complex and dynamic,[25] and the reduction of one factor (i.e. time-dependent ventilation–perfusion mismatching) obtained with the manoeuvres did not reduce these variations. The decrease in arterial to end-expiratory difference obtained with both manoeuvres suggests that temporal deadspace (related to the phasic variations in ventilation and perfusion during controlled ventilation, and which one would anticipate to be increased during prolonged expiration manoeuvres) was less important than spatial, between- and within-units mismatching.[16] However, inter-individual differences in temporal ventilation–perfusion mismatching during the manoeuvres may have contributed to their poor reliability.

In summary, we have confirmed that prolonged expiration manoeuvres reduced the mean arterial to peak expired carbon dioxide partial pressure difference. However, the end-expiratory $PCO_2$ obtained with each manoeuvre agreed poorly with $Pa_{CO_2}$. This suggests that these manoeuvres should no longer be recommended to improve estimation of $Pa_{CO_2}$ from $PE'_{CO_2}$ during anaesthesia.

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# Inositol 1,4,5-trisphosphate in blood and skeletal muscle in human malignant hyperthermia†

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**Summary**

The *in vitro* contracture test (IVCT) is the only available diagnostic method at present for evaluation of malignant hyperthermia (MH) susceptibility. However, the disadvantage of the IVCT is that it is invasive. Several studies suggest that an altered inositol phosphate system is involved in the development of MH. A greater concentration of inositol 1,4,5-trisphosphate (1,4,5-IP$_3$) was found in MH susceptible (MHS) than in normal (MHN) skeletal muscles. In this study the concentrations of 1,4,5-IP$_3$ in blood samples and skeletal muscle specimens of identical patients were measured in an attempt to define susceptibility to MH. Muscle biopsies were obtained from 34 patients with clinical suspicion of MH. Patients were first classified as MHS ($n$=19), MHN ($n$=8) or MH equivocal (MHE; $n$=7) by the standard IVCT. For detection of 1,4,5-IP$_3$ concentrations, blood samples were obtained and an additional muscle specimen was excised. After sample preparation, concentrations of 1,4,5-IP$_3$ were measured using radioimmunoassay. In blood samples, concentrations of 1,4,5-IP$_3$ were similar in all individuals tested for MH susceptibility and in control patients not tested for MH susceptibility ($n$=44). In skeletal muscle, 1,4,5-IP$_3$ concentrations were significantly higher in MHS than in MHE or MHN patients, respectively. Each MHS sample contained more 1,4,5-IP$_3$ than the highest concentration measured in MHN muscle. Defining arbitrary thresholds for 1,4,5-IP$_3$ concentration in skeletal muscles in order to discriminate between MHS and MHN status, it was possible to assign three MHE patients to MHS and four to MHN. This study supports the hypothesis that an altered inositol phosphate system might be involved in MH. However, measurement of 1,4,5-IP$_3$ concentration in a simple blood sample preparation is not reliable for MH susceptibility screening. (*Br. J. Anaesth.* 1997; **78**: 541–547).

**Key words**
Anaesthetics volatile, halothane. Malignant hyperthermia Metabolism, inositol phosphate. Muscle skeletal. Screening.

Susceptibility to malignant hyperthermia (MH) in humans is diagnosed by *in vitro* contracture tests (IVCT) using halothane and caffeine on skeletal muscle specimens obtained at open biopsy.[1 2] In 1970 caffeine was introduced as the test drug for MH susceptibility followed by halothane 1 yr later.[3 4] Both caffeine and halothane produce abnormal contracture responses in muscle specimens obtained from MH susceptible (MHS) but not from normal (MHN) individuals. At present, the IVCT using caffeine and halothane is generally accepted as the "gold standard" for diagnosis of MH susceptibility. However, the major disadvantage of the IVCT is that it is invasive. Therefore, it would be desirable to have an accurate, non-invasive, low-cost screening test for MH susceptibility.

Skeletal muscle cells from MHS individuals have an inherited abnormality in the processes that are involved in the excitation–contraction coupling or myoplasmic calcium regulation,[5 6] leading to a rapid and sustained increase in myoplasmic calcium during anaesthetic-induced MH crisis. Intracellular calcium concentrations are controlled by different types of calcium release channels, that is the ryanodine receptor in the terminal cisternae of the sarcoplasmic reticulum (SR), the dihydropyridine receptor in the transverse tubule and the inositol-1,4,5-trisphosphate receptor.[6 7] In pigs, the defect predisposing to MH susceptibility is associated with the ryanodine receptor, possibly because of a specific breeding effect,[8 9] whereas the detailed molecular mechanisms leading to the human MH syndrome are still unknown. Recent studies indicated that a second factor or modulator is required for expression of the MH syndrome in humans.[10] Furthermore, dysfunction in the phosphoinositide pathway and metabolism of free fatty acids have been proposed as underlying causes of the alterations in calcium regulation in MH.[11–13] The second messenger inositol-1,4,5-trisphosphate (1,4,5-IP$_3$) has a key role in controlling both mobilization of calcium from internal stores and entry of external calcium.[14] As increased concentrations of 1,4,5-IP$_3$ were found in

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MHS individuals[12] and also in MHS swine,[11] there is an increasing number of reports indicating that an altered inositol phosphate system is involved in the development of MH.[15–18] However, in skeletal muscle the sensitivity of the intracellular $Ca^{2+}$ release mechanism to 1,4,5-$IP_3$ is highly dependent on experimental conditions, and this had led to conflicting views on the role of the phosphoinositide pathway in muscle.[19]

In this study we have measured basal concentrations of 1,4,5-$IP_3$ in blood samples and skeletal muscle specimens to determine if 1,4,5-$IP_3$ concentration in blood samples from patients with clinical suspicion of MH might be a reliable non-invasive screening test for MH classification. The second aim of this study was to see if a combination of a ryanodine contracture test and measurement of 1,4,5-$IP_3$ concentrations in skeletal muscle specimens could be helpful in assigning MHE patients to MHS and MHN groups.

## Patients and methods

The study was approved by the local Ethics Committee and written informed consent was obtained from patients and their parents, if appropriate. We studied 34 patients from 19 families, 23 adults and 11 children, aged 7–44 yr, with a clinical suspicion of MH. Before starting the investigation, a personal and family history was obtained from all patients. Before operation, blood samples for measurement of 1,4,5-$IP_3$ concentration were obtained from all patients, and also from 44 control subjects without a history of MH.

### MUSCLE BIOPSIES

Adult muscle biopsies were obtained under regional anaesthesia (3-in-1 nerve block) with 1% prilocaine 40 ml. Biopsies in children were excised under general anaesthesia. Patients received midazolam 0.1 mg $kg^{-1}$ orally, 2 h before induction of anaesthesia. Anaesthesia was induced with alfentanil 50 $\mu g\ kg^{-1}$ i.v. followed by propofol 2–2.5 mg $kg^{-1}$. Before laryngoscopy and tracheal intubation, vecuronium 0.1 mg $kg^{-1}$ was given i.v. A continuous infusion of propofol $\geq 150\ \mu g\ kg^{-1}\ min^{-1}$ and 66% nitrous oxide in oxygen was used for maintenance of anaesthesia. Two or three muscle bundles were excised carefully from the vastus lateralis. The fresh specimens were placed in a container filled with carboxygenated Krebs–Ringer solution of the following composition (mmol $litre^{-1}$): NaCl 118.1; KCl 3.4; $CaCl_2$ 2.5; $MgSO_4$ 0.8; $KH_2PO_4$ 1.2; $NaHCO_3$ 25.0; and glucose 11.1, and transported to our laboratory. Apart from these specimens, an additional muscle sample (weight 200–400 mg) was excised for measurement of 1,4,5-$IP_3$ concentration. Before cutting the fibres, the muscle specimen was clamped, and immediately after excision the samples were frozen in liquid nitrogen and stored at −80 °C.

### *IN VITRO* CONTRACTURE TEST

The muscle bundles were dissected into 6–8 strips (length 15–25 mm; width 2–3 mm; weight 100–250 mg). All tests were performed within 5 h after biopsy. The muscle strips were suspended in an 80-ml organ bath perfused with Krebs–Ringer solution bubbled with carbogen continuously, temperature was kept constant at 37 °C and pH was adjusted to 7.4. Isometric tension was amplified by a Gould THE (Cleveland, OH, USA) and recorded on a Gould polygraph TA 2000 (Cleveland, OH, USA) using a Fleck TF 3V force displacement transducer (Mainz, Germany). The muscles were stimulated electrically to achieve a supramaximal response by a Grass Stimulator SD 9 (Quincy, MA, USA) using a square wave with a duration of 1 ms and a frequency of 0.2 Hz. An initial baseline tension of 20 mN was applied. Two specimens were investigated simultaneously.

Patients were classified first as MHS, MHN or MHE (MH equivocal) by the IVCT with caffeine and halothane, according to the procedure of the European Malignant Hyperthermia Group (EMHG).[1] The IVCT gave halothane and caffeine thresholds for each patient as follows: MHS=muscle contractures ≥2 mN (corresponding to ≥0.2 g in the original version of the procedure) at a caffeine concentration of 2.0 mmol $litre^{-1}$ or less *and* at a halothane threshold concentration of 0.44 mmol $litre^{-1}$ or less; MHN=muscle contractures ≥2 mN at a caffeine concentration of 3.0 mmol $litre^{-1}$ or more *and* at a halothane threshold concentration greater than 0.44 mmol $litre^{-1}$; MHE=patients with an abnormal contracture response either to caffeine (MHEc) or halothane (MHEh).

### ANALYSIS OF INOSITOL 1,4,5-TRISPHOSPHATE CONCENTRATIONS

Frozen muscle samples were powdered in a liquid nitrogen cooled dismembranator (Braun Melsungen, Germany) and the wet weight of the samples was measured. Subsequently, muscle and blood samples were mixed with 0.2 volume ice-cold 20% perchloric acid and kept on ice for 20 min. Proteins were sedimented by centrifugation at 2000 *g* for 15 min at 4 °C. Supernatants were adjusted to a pH of 7.5 by addition of 10 N KOH and kept ice-cold. Precipitated $KClO_4$ was sedimented and removed by centrifugation. Samples were neutralized by adding 300 µl of a 1:1 (v/v) of Freon (1,1,2-trichlorotrifluoroethane) and tri-n-octylamine, followed by vigorous mixing of the separate phases on a vortex mixer. After centrifugation for 1 min at 2000 *g*, three phases were obtained. A 400-µl portion of the upper phase, which contained the neutralized sample, was removed for subsequent analysis. After addition of the assay buffer (D-myo-[$^3H$] inositol-1,4,5-trisphosphate) and 1,4,5-$IP_3$ binding protein, samples were incubated for 15 min and centrifuged. After decanting and discarding the supernatant, the pellets were resuspended and 2 ml of scintillant added to each tube. Subsequently, radioactivity was measured in a β-scintillation counter. For calculation of the results a standard curve, generated by plotting the percent $B/B_0$ as a function of $\log_{10}$ 1,4,5-$IP_3$ concentration was used.

RYANODINE CONTRACTURE TEST

After the IVCT, surplus muscle specimens were used in the ryanodine contracture test for diagnosis of MH susceptibility, as described recently.[20] Ryanodine was added as a bolus to the organ bath in order to obtain a concentration of 2 μmol $litre^{-1}$. The development of contracture after ryanodine administration was characterized by attainment of three phases: (1) start of contracture (min); (2) time (min) when contracture reached 2 mN; and (3) time (min) when contracture reached 10 mN. With the results for MHS and MHN after ryanodine 2 μmol $litre^{-1}$, we arbitrarily defined time intervals to assign MHE patients to either the MHS or MHN group, respectively.

The following chemicals were used: caffeine (Sigma, Deisenhofen, Germany), halothane (Hoechst, Frankfurt, Germany), ryanodine (purity >99% by HPLC; Calbiochem, La Jolla, USA). All substances were prepared freshly, dissolved in pre-warmed and pre-gassed Krebs–Ringer solution at 37°C and added directly to the organ bath. Halothane was added to carbogen from a Dräger vaporizer (Lübeck, Germany); the concentration of halothane was measured with an anaesthetic gas monitor (Normac, Datex, Helsinki, Finland). Bath concentration of halothane was measured by gas chromatography.[21]

STATISTICAL ANALYSIS

Data are presented as median, range and SD (patients characteristics). Values were analysed using the Kruskal–Wallis and Mann–Whitney non-parametric tests to determine differences between groups. Results were considered significant if $P<0.05$.

## Results

Nineteen patients were classified as MHS, eight as MHN and seven as MHE, according to the IVCT criteria of the European MH Group. Patient characteristics did not differ significantly (see table 1), but because one MHE patient had a creatine kinase (CK) concentration of 1800 iu $litre^{-1}$, CK values at rest were significantly greater in the MHE (315.7 (615.5) iu $litre^{-1}$) than in the MHS (61.6 (28.3) iu $litre^{-1}$) and MHN (55.6 (27.1) iu $litre^{-1}$) groups.

In simple blood sample preparations, 1,4,5-$IP_3$ concentrations were similar in all individuals tested for MH susceptibility and in control patients (fig. 1). Concentrations of 1,4,5-$IP_3$ in the MHS group ranged from 4.3 to 11.6 (median 8.7) pmol/tube. In the MHE group, values were 5.1–12.5 (median 9.9) pmol/tube. Median 1,4,5-$IP_3$ concentrations in the MHN group (5.5 pmol/tube) were smaller than those in the other groups. However, the range (4.0–11.0 pmol/tube) did not differ significantly from concentrations in the MHS and MHE groups. The control population showed a homogeneous distribution with a minimum of 3.4 and a maximum of 12.0 pmol/tube, which were similar to the results of the MH patients.

In skeletal muscles from the same patients, there were significant differences in 1,4,5-$IP_3$ concentrations (fig. 2). The median in the MHS group (6.2 pmol/mg ww) was significantly higher than that in the MHN group (1.7 pmol/mg ww). The ranges in both groups also showed marked differences: 1,4,5 $IP_3$-concentrations in the MHN group were 0.2–2.8 pmol/mg ww compared with 2.9–12.8 pmol/mg ww in the MHS group. Concentrations of 1,4,5-$IP_3$ in MHE individuals were between those of the MHS and MHN subjects, and were significantly different

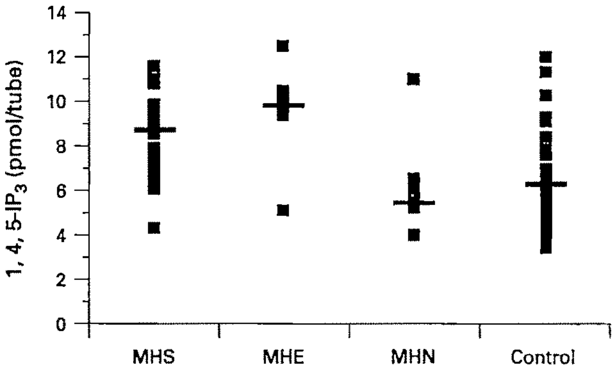

*Figure 1* Median (—) and individual (■) concentrations of inositol 1,4,5-trisphosphate (1,4,5-$IP_3$) measured in blood samples from MHS ($n$=19), MHE ($n$=7) and MHN ($n$=8) patients, and in controls ($n$=44).

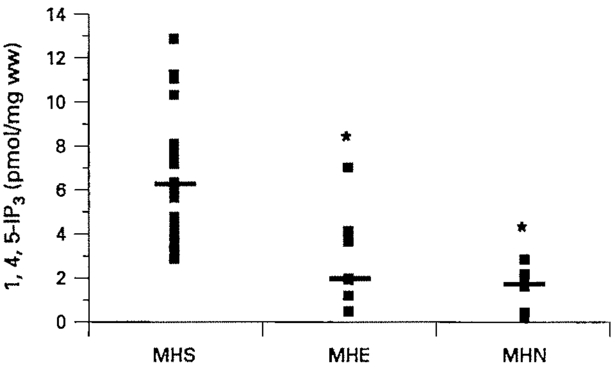

*Figure 2* Median (—) and individual (■) concentrations of inositol 1,4,5-trisphosphate (1,4,5-$IP_3$) measured in skeletal muscle specimens from MHS ($n$=19), MHE ($n$=7) and MHN ($n$=8) patients. *$P<0.05$ compared with MHS.

*Table 1* Patients characteristics (mean (SD) [range]) *$P<0.05$ compared with MHN

| | MHS ($n$=19) | MHE ($n$=7) | MHN ($n$=8) |
|---|---|---|---|
| Age (yr) | 27 [7–44] | 30 [7–45] | 19 [9–30] |
| Sex (M/F) | 11/8 | 4/3 | 3/5 |
| Weight (kg) | 59 (19.2) [24–85] | 64 (20.3) [25–87] | 59 (17.4) [26–85] |
| Height (cm) | 163 (18 4) [128–190] | 169 (19.8) [130–189] | 162 (15.3) [125–178] |
| Creatine kinase (iu $litre^{-1}$) | 61.6 (28.3) [18–106] | 315.7 (615.5) [26–1800]* | 55.6 (27.1) [27–110] |

*Table 2* Contractures after bolus administration of ryanodine 2 $\mu$mol litre$^{-1}$ in skeletal muscle specimens of malignant hyperthermia susceptible (MHS), equivocal (MHE) and non-susceptible (MHN) patients. Hal. thresh.=threshold tension for halothane; Caff. thresh.=threshold tension for caffeine. OT=onset time of contracture; 2 mN=contracture reaches 2 mN; 10 mN=contracture reaches 10 mN. *($P<0.05$)compared with MHS

| Patient No. | Hal. thresh. (mmol litre$^{-1}$) | Caff. thresh. (mmol litre$^{-1}$) | Muscle twitch (mN) | OT (min) | 2 mN (min) | 10 mN (min) |
|---|---|---|---|---|---|---|
| MHS | | | | | | |
| 1 | 0.44 | 1.0 | 42.0 | 1.6 | 6.0 | 10.7 |
| 2 | 0.22 | 2.0 | 63.0 | 3.0 | 7.2 | 13.0 |
| 3 | 0.22 | 1.0 | 29.0 | 2.5 | 4.7 | 7.6 |
| 4 | 0.22 | 1.0 | 51.0 | 3.4 | 6.9 | 9.1 |
| 5 | 0.22 | 1.0 | 37.0 | 1.1 | 3.8 | 9.5 |
| 6 | 0.11 | 1.0 | 25.0 | 0.8 | 2.0 | 3.3 |
| 7 | 0.44 | 1.5 | 22.0 | 3.2 | 10.5 | 17.6 |
| 8 | 0.44 | 2.0 | 99.0 | 3.2 | 8.3 | 13.4 |
| 9 | 0.22 | 2.0 | 43.0 | 1.0 | 2.8 | 12.9 |
| 10 | 0.44 | 2.0 | 52.0 | 1.7 | 8.7 | 17.8 |
| 11 | 0.44 | 2.0 | 56.0 | 1.2 | 7.3 | 17.7 |
| 12 | 0.44 | 2.0 | 23.0 | 2.5 | 10.0 | 14.0 |
| 13 | 0.44 | 2.0 | 47.0 | 2.3 | 8.8 | 15.6 |
| 14 | 0.44 | 2.0 | 32.0 | 3.2 | 9.6 | 14.4 |
| 15 | 0.44 | 1.5 | 15.0 | 2.4 | 8.9 | 15.0 |
| 16 | 0.22 | 1.0 | 25.0 | 3.0 | 8.0 | 12.3 |
| 17 | 0.11 | 0.5 | 61.0 | 1.9 | 3.6 | 5.4 |
| 18 | 0.44 | 2.0 | 49.0 | 3.5 | 9.8 | 12.6 |
| 19 | 0.22 | 1.5 | 36.0 | 3.0 | 9.2 | 17.5 |
| Median | 0.44 | 1.5 | 42.0 | 2.5 | 8.0 | 13.0 |
| MHE | | | | | | |
| 1 | — | 1.5 | 22.0 | 1.3 | 5.8 | 9.8 |
| 2 | — | 2.0 | 17.0 | 12.5 | 18.0 | 23.3 |
| 3 | — | 2.0 | 54.0 | 3.8 | 11.4 | 18.2 |
| 4 | 0.44 | 4.0 | 31.0 | 2.0 | 6.8 | 14.1 |
| 5 | 0.44 | 32.0 | 62.0 | 3.1 | 5.9 | 9.2 |
| 6 | — | 2.0 | 48.0 | 11.6 | 17.1 | 23.5 |
| 7 | — | 1.5 | 35.0 | 4.7 | 15.8 | 23.4 |
| Median | — | 2.0 | 35.0 | 3.8* | 11.4 | 18.2 |
| MHN | | | | | | |
| 1 | — | 3.0 | 24.0 | 6.6 | 11.8 | 18.0 |
| 2 | — | 3.0 | 28.0 | 8.6 | 15.1 | 26.7 |
| 3 | — | 3.0 | 53.0 | 7.9 | 12.1 | 18.3 |
| 4 | — | 3.0 | 59.0 | 5.8 | 14.8 | 19.7 |
| 5 | — | 3.0 | 75.0 | 5.7 | 17.9 | 30.1 |
| 6 | — | 3.0 | 47.0 | 5.3 | 13.0 | 20.0 |
| 7 | — | 3.0 | 54.0 | 8.8 | 16.2 | 25.8 |
| 8 | — | 3.0 | 21.0 | 6.1 | 12.4 | 19.9 |
| Median | — | 3.0 | 30.5 | 6.4* | 13.9* | 20.0* |

from the MHS results. Individual data for three MHE patients varied from 3.7 to 7.0 pmol/mg ww, corresponding to the range of values for MHS, and four values varied from 0.5 to 2.0 pmol/mg ww, corresponding to MHN.

Individual data for contracture testing using ryanodine 2 $\mu$mol litre$^{-1}$ are presented in table 2. Contracture development after ryanodine administration was enhanced significantly in MHS compared with MHN muscles. Median values for MHE muscles were always between those of MHS and MHN.

Table 3 summarizes the results of the IVCT, 1,4,5-IP$_3$ concentrations in skeletal muscle and the ryanodine contracture test in MHE patients. In an attempt to assign MHE muscles to either the MHS or MHN group, we arbitrarily defined thresholds for 1,4,5-IP$_3$ concentrations in skeletal muscles of $\geq$2.9 pmol/mg ww for MHS and $\leq$2.8 pmol/mg ww for MHN. Thus an assignment of three MHE patients to the MHS group was possible. MHE patient Nos 1, 3, 6 and 7 were defined as MHN. Using the range of values for MHS and MHN according to the ryanodine contracture test, we arbitrarily defined intervals to categorize MHE muscles as either MHS or MHN, as described recently.[20] Three MHE muscles showed enhanced contracture development and were classified as MHS. In four muscles a marked delay in contracture development occurred and these were allocated to the MHN group. In five

*Table 3* Results of *in vitro* contracture tests with halothane and caffeine (IVCT), measurement of inositol 1,4,5-trisphosphate (1,4,5-IP$_3$) concentration in skeletal muscles and the ryanodine contracture test (RCT) using ryanodine at a concentration of 2 $\mu$mol litre$^{-1}$ in malignant hyperthermia equivocal (MHE) patients

| Patients No. | IVCT | 1,4,5-IP3 (pmol/mg ww) | RCT |
|---|---|---|---|
| 1 | MHE | MHN (0.5) | MHS |
| 2 | MHE | MHS (4.1) | MHN |
| 3 | MHE | MHN (2.0) | MHN |
| 4 | MHE | MHS (3.7) | MHS |
| 5 | MHE | MHS (7.0) | MHS |
| 6 | MHE | MHN (1.2) | MHN |
| 7 | MHE | MHN (1.9) | MHN |

of seven MHE muscles, consistent results in both tests were observed. The same MH classification was possible using measurement of 1,4,5-$IP_3$ concentrations and ryanodine contracture testing.

## Discussion

We have found that 1,4,5-$IP_3$ concentrations in skeletal muscle specimens were significantly higher in MHS than in MHN patients. In contrast, 1,4,5-$IP_3$ concentrations in blood samples of the same patients and controls did not differ. Thus it was possible to differentiate between MHS and MHN individuals by measurement of 1,4,5-$IP_3$ concentrations in skeletal muscle specimens but not in simple blood sample preparations. Furthermore, we have demonstrated that a combination of a ryanodine contracture test and measurement of 1,4,5-$IP_3$ concentrations in skeletal muscle specimens could be helpful in assigning MHE patients to MHS and MHN groups.

For evaluation of susceptibility to MH, only the *in vitro* contracture tests with halothane and caffeine have been shown to be reliable in distinguishing between MHS and MHN individuals. Human skeletal muscle contracture testing for diagnosis of MH susceptibility seems to be highly sensitive.[22] However, the specificity of the IVCT was estimated as 80–85%.[23] For the first time in 1993 four cases were described of presumably false-negative contracture responses in muscle specimens from patients with a clinical history of MH.[24] However, there is considerable debate about these cases because the authors did not use the EMHG test procedure; in two cases there was no clinical evidence of MH and muscle histology and neurological examination were not performed in all patients. Four additional cases were presented recently of false-negative IVCT results in juvenile patients surviving MH episodes during general anaesthesia.[25] The authors suggested that the age of the patients might have affected the contracture results. However, whereas in newborn MHS piglets decreased responsiveness to halothane compared with mature animals has been observed,[26] age dependence of MH in humans has not been demonstrated until now.

The caffeine contracture test produces false-negative results in approximately 15% of MH susceptible patients. Moreover, both caffeine and the halothane tests were shown not to be specific for MH, as positive IVCT results were observed in some individuals with other muscle disorders.[27] Contracture test results in control patients suggested a false-positive rate of approximately 4% using the European[28] and 9% using the North American MH procedures.[23] The hypothesis that MH is caused by an abnormal ryanodine receptor gene focused interest on developing an alternative test for diagnosis of MH using ryanodine. *In vitro* studies of ryanodine-induced contractures showed that in muscle specimens of MHS patients, contractures developed significantly earlier than in specimens from MHN individuals.[20 29–32] Although the results of contracture testing with ryanodine in conjunction with the standard halothane and caffeine contracture tests could improve diagnosis of MH susceptibility,[33] the ryanodine contracture test is also not specific for MH. Moreover, the disadvantage of contracture testing with halothane, caffeine and ryanodine is that it is invasive, time consuming and expensive.

Since the identification of the ryanodine receptor gene, thought to be responsible for MH,[34 35] it has been assumed that MH susceptibility could be detected using a genetic test based on DNA analysis. Molecular genetic studies have shown that a single point mutation in the ryanodine receptor gene (C1843-T mutation) is frequently correlated with MH in swine.[9] However, the corresponding mutation in the human genom (C1840-T mutation) was detected first in only one of 35 MH families.[36] At present, the frequency of this single point mutation in the human ryanodine receptor gene has been calculated to be less than 10%.[10 37] Moreover, mutation screening of the ryanodine receptor gene in MHS individuals has led to the identification of seven other mutations to date.[38] Furthermore, genetic heterogeneity has been reported in MH[39] and several additional MHS loci on chromosomes 17, 7 and 3.[40–42] DNA-based testing in MH would be non-invasive, accurate and less expensive, but there is little probability that a universal genetic test for MH susceptibility in humans will be easily developed because of heterogeneity, increasing number of identified mutations in MH and association with muscle cell deficiencies induced by other neuromuscular diseases.

Activation of G protein-linked receptors led to the dissociation of the G protein in the subunits $G_\alpha$ and $G_{\beta\gamma}$, both of which can activate different phospholipase C (PLC) enzymes.[14] In energy-requiring transducing mechanisms, PLC hydrolyses the lipid precursor phosphatidylinositol 4,5-bisphosphate to stimulate formation of both diacylglycerol (DAG) and 1,4,5-$IP_3$, which binds to an 1,4,5-$IP_3$ receptor to mobilize stored $Ca^{2+}$. It is believed that abnormal regulation of intracellular $Ca^{2+}$ concentration within skeletal muscle is the process of primary significance in MH episodes. Furthermore, malfunctions in the phosphoinositide cycle and free fatty acid metabolism were shown to be associated with MH susceptible muscle.[11–13 16–18] Basal concentrations of 1,4,5-$IP_3$ in skeletal muscles of MHS swine[11] and humans[12] were found to be significantly higher than in MHN. It was demonstrated that successive additions of 1,4,5-$IP_3$ induced short pulses of calcium release.[43] Moreover, microinjection of 1,4,5-$IP_3$ increased intracellular $Ca^{2+}$ in intact skeletal muscle from MHS swine with higher potency and efficacy than in muscles from MHN swine.[15] Dantrolene decreased resting intracellular $Ca^{2+}$ concentration and prevented 1,4,5-$IP_3$-induced increase in intracellular $Ca^{2+}$. These results suggest that skeletal muscle fibres from MHS have a higher sensitivity to 1,4,5-$IP_3$-induced regulation of intracellular $Ca^{2+}$, which could play an important role in MH induction. In the presence of halothane, 1,4,5-$IP_3$-concentration increased to a higher extent in MHS than in MHN muscles.[11] Moreover, it has been shown that halothane challenge caused an increase in the second messengers 1,4,5-$IP_3$ and 1,3,4,5-$IP_4$ in MHS but not in MHN swine.[18] Treatment with dantrolene reduced the increase to values close to basal concentrations. To date, it is not clear if the alterations in phosphoinositide metabolism are primary in MH induction or of a secondary nature. ATP at low concentrations enhances the ability of 1,4,5-$IP_3$ to open $Ca^{2+}$ channels in the SR membrane. It has been hypothesized that the lower the ATP concentration, possibly as a result of the hypermetabolic state of MH, and the higher the 1,4,5-$IP_3$ concentration, the more $Ca^{2+}$ is released.[17] It has been speculated therefore that measurement of $Ca^{2+}$ or 1,4,5-$IP_3$ concentrations, or both, in muscle but also in non-muscle cells, could be used for diagnosing MH susceptibility.[44–46] However, the differences in these investigations were not reliable in determining susceptibility to MH until now.[46] Moreover, in accordance with our data from simple blood sample preparations, no differences in 1,4,5-$IP_3$ concentrations in human red blood cells were observed between MHS and MHN.[47]

In summary, this study supports the hypothesis that an altered inositol phosphate system might be involved in MH. One might speculate that the differences between skeletal muscles might also exist in other cell types, including blood cells. Further investigations are required to develop an accurate, reliable, low-cost and non-invasive screening test. Such a test might be measurement of 1,4,5-$IP_3$ concentration in different blood components or cell types, or methods of detecting genetic defects in 1,4,5-$IP_3$ metabolism.

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LABORATORY INVESTIGATIONS

# Leucocyte-derived bioactive substances in fresh frozen plasma

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## Summary

Bioactive substances in fresh frozen plasma (FFP) are considered to be related to adverse reactions after transfusion, particularly in septic or traumatized patients. Therefore, we analysed the concentration of various bioactive substances (histamine, eosinophil cationic protein, eosinophil protein X, myeloperoxidase and interleukin-6) in 25 u. of thawed FFP from healthy donors. These were compared with donor plasma concentrations of 24 healthy controls. In addition, we analysed the concentration of the bioactive substances, except interleukin-6, in 25 u. of thawed FFP, which were subjected to leucocyte filtration before freezing and storage. Finally, we analysed the substances in 10 leucocyte non-filtered plasma units before freezing and storage, and after thawing, respectively. Before analyses, which were performed by ELISA and RIA methods, these latter samples were sterile filtered through a 0.20-μm filter. Histamine, eosinophil cationic protein, eosinophil protein X and myeloperoxidase concentrations were significantly greater ($P<0.05$) in the 25 u. of FFP compared with normal donor plasma. Pre-storage leucocyte filtration reduced concentrations of the bioactive substances in FFP to concentrations comparable with normal donor plasma concentrations. Interleukin-6 was undetectable in all FFP units and in 21 of the 24 control donors. Histamine, eosinophil cationic protein and myeloperoxidase concentrations were significantly higher ($P<0.05$) in samples collected from the 10 u. of FFP after freezing and thawing compared with samples collected before freezing. We conclude that fresh frozen plasma prepared by a conventional separation method contains various leucocyte-derived bioactive substances, which may be reduced by pre-storage leucocyte filtration. (*Br. J. Anaesth.* 1997; **78**: 548–552).

**Key words**
Blood, fresh frozen plasma. Blood, transfusion. Blood, leucocytes. Immune response.

Blood transfusion therapy has changed from whole-blood products towards component therapy, and plasma preparations are at present a valuable component in massive transfusion regimens. The interest in transfusion-induced detrimental effects has focused primarily on leucocyte-containing blood products.[1 2] Evidence has emerged, however, suggesting that plasma and plasma derivatives contribute to adverse reactions in transfusion therapy.[3 4] The mechanisms of plasma component-induced adverse effects are largely unknown, but plasma proteins, alloantigens, alloantibodies and undefined bioactive substances, particularly in fresh frozen plasma (FFP), may participate in post-transfusion adverse reactions.[3 4] Thus FFP may play a role in transfusion-related acute lung injury (TRALI),[5] adult respiratory distress syndrome (ARDS),[6] febrile non-haemolytic transfusion reaction (FNHTR),[3 4] fatal shock in septicaemia[7] and possibly in immunosuppression.[8]

Previously, we showed time-dependent cumulation of histamine, eosinophil cationic protein (ECP), eosinophil protein X (EPX), myeloperoxidase (MPO) and plasminogen activator inhibitor-1 (PAI-1) from basophils, eosinophils, neutrophils and platelets, respectively, in supernatants from various erythrocyte suspensions during storage.[9 10] Fresh plasma contains approximately $5\times10^5$ leucocytes per unit, while leucocytes are undetectable in FFP thawed before clinical use.[3] This suggests that leucocytes contaminating FFP are totally lysed and therefore may have released their preformed bioactive substances contained within intracellular granules.

The purpose of this study was to evaluate concentrations of various leucocyte- and platelet-derived bioactive substances in FFP. In addition, we studied the effect of pre-storage leucocyte filtration on concentrations of bioactive substances.

## Subjects and methods

Peripheral venous blood (4.5 ml) was obtained from 24 randomly selected normal donors to establish

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normal plasma concentrations of histamine, ECP, EPX, MPO, PAI-1 and interleukin-6 (IL-6). Blood was obtained into ice-chilled endotoxin-free glass tubes (Beckon-Dickinson, Mountain View, CA, USA) containing 0.5 ml of sodium citrate 0.129 mol $\text{litre}^{-1}$ and aprotinin 12.5 kiu $\text{ml}^{-1}$. Sodium citrate was used as an anticoagulant because of the recent finding of contamination of heparin preparations by histamine,[11] and because sodium citrate is used in standard blood bags (Baxter SA, La Chatre, France) at our institution. Subsequently, blood was centrifuged at +4 °C at 1200 *g* for 10 min. Plasma was separated carefully from cells and frozen at −70 °C.

FFP was prepared from 450 ml of blood donated into blood bags (Baxter SA) containing 63 ml of citrate, phosphate and dextrose solution (CPD) as anticoagulant. Within 1 h after donation, fresh plasma was separated from red cells and buffy-coat by centrifugation of the blood bag at 5000 *g* for 8 min, followed by transfer of plasma to a separate bag containing 280±10 ml of plasma. Finally, plasma was quick-frozen in absolute alcohol at −39.4 °C and stored at −25 °C until use. In addition, 25 other units of plasma prepared from whole blood by a similar procedure were subjected to leucocyte filtration before freezing and storage, using the LPS2E leucocyte filter (Pall Biomedicals Ltd, Portsmouth, UK). The filter was connected between the plasma bag and the empty bag by using a sterile welding technique.

We obtained samples (5.0 ml in endotoxin-free plastic tubes, Beckon-Dickinson) from 25 u. of leucocyte non-filtered and 25 u. of leucocyte-filtered FFP, respectively, before transfusion to burn trauma patients. The samples were collected after FFP had been thawed in a water bath at +37 °C for 30 min, kept on ice, and subsequently frozen at −70 °C until analysis.

Samples were also collected from 10 additional plasma units before freezing. These samples (5.0 ml) were centrifuged at +4 °C at 5000 *g* for 15 min and only the top 80% of the plasma of each tube was collected for analyses. Thereby, the bottom 20% of the plasma, which may contain cellular debris, was not used for analyses. To assure complete absence of free leucocyte granules in samples for analyses, plasma was sterile-filtered using a 0.20-μm filter (Sterile AerodiscR, Gelman Sciences Inc., Ann Arbor, MI, USA). Subsequently, the 10 u. of plasma were frozen and thawed as described previously, and the sample, centrifugation, separation and sterile filtration procedures were repeated.

When all samples were collected, normal plasma and FFP concentrations of histamine were analysed using a commercially available ELISA method (Immunotech SA, Marseilles, France) as described previously[9] (detection limit=0.5 nmol $\text{litre}^{-1}$). ECP and EPX were analysed using ELISA methods[12,13] (detection limits=15 pg $\text{ml}^{-1}$ and 60 pg $\text{ml}^{-1}$, respectively). MPO and IL-6 were analysed using commercially available RIA (MPO RIA, Pharmacia AB, Uppsala, Sweden) and ELISA (IL-6, Immunotech SA, Marseilles, France) methods (detection limits=8 ng $\text{ml}^{-1}$ and 3.9 pg $\text{ml}^{-1}$, respectively). In addition, PAI-1 from platelets was analysed in supernatants from the 10 u. of FFP before freezing and after thawing to detect eventual platelet contamination of FFP. PAI-1 was analysed by an ELISA method[14] with a detection limit of 20 pg $\text{ml}^{-1}$. All analyses were performed in duplicate.

Differences between normal donor plasma concentrations and FFP concentrations before transfusion, and differences in concentrations in plasma samples before and after freezing–thawing were evaluated statistically using the Mann–Whitney test. All values are given as median (range). $P<0.05$ was considered significant.

## Results

Median donor plasma concentrations of histamine, ECP, EPX, MPO and IL-6 are shown in table 1. Plasma concentrations of IL-6 were below the detection limit (3.9 pg $\text{ml}^{-1}$) in 21 of the 24 control donors.

Concentrations of histamine, ECP, EPX, MPO and IL-6 in leucocyte non-filtered FFP and histamine, ECP, EPX and MPO concentrations in leucocyte-filtered FFP are also shown in table 1. Histamine ($P<0.05$), ECP ($P<0.05$), EPX ($P<0.05$) and MPO ($P<0.01$) concentrations were significantly higher in leucocyte non-filtered FFP compared with donor plasma concentrations and with concentrations in leucocyte-filtered FFP. Interleukin-6 was not analysed in leucocyte-filtered FFP because it was undetectable in non-filtered FFP.

Donor blood for analysis of plasma bioactive substance concentrations was diluted 1:10 by sampling 4.5 ml of blood in 0.5 ml of sodium citrate and aprotinin. Thereby, control donor plasma concentrations may be diluted by 1:6.4 when using an average packed cell volume of 0.4. Similarly, donor blood (450 ml) was diluted by 63 ml of CPD in the bags, and when using a mean packed cell volume of 0.4, the substance concentration in FFP may be

*Table 1* Donor plasma and fresh frozen plasma (FFP) concentrations of various bioactive substances (median (range)). $^{*}P<0.05$ *vs* donor plasma and leucocyte-filtered FFP; $^{**}P<0.01$ *vs* donor plasma and leucocyte-filtered FFP. nd=Not determined

| | Donor plasma (*n*=24) | FFP (non-filtered) (*n*=25) | FFP (leucocyte-filtered) (*n*=25) |
|---|---|---|---|
| Histamine (nmol $\text{litre}^{-1}$) | 5.1 (3.9–9.1) | 11.3 (6.4–32.0)* | 6.2 (3.5–11.0) |
| ECP (ng $\text{ml}^{-1}$) | 1.3 (0.5–8.1) | 2.8 (1.9–12.8)* | 1 1 (0.6–7.3) |
| EXP (ng $\text{ml}^{-1}$) | 11.1 (5.9–17.5) | 19.1 (10.9–40.4)* | 12.0 (6.2–19.1) |
| MPO (ng $\text{ml}^{-1}$) | 179 (96–344) | 691 (361–1152)** | 205 (107–429) |
| IL-6 (pg $\text{ml}^{-1}$) | 0 (0–30) | 0 (0) | nd |

*Table 2* Concentrations of various bioactive substances in plasma before freezing and after thawing (median (range)). *$P<0.05$; **$P<0.01$

| | Before freezing ($n=10$) | After thawing ($n=10$) |
|---|---|---|
| Histamine (nmol litre$^{-1}$) | 6.6 (3.1–9.4) | 15.8 (6.2–52.1)* |
| ECP (ng ml$^{-1}$) | 1.0 (0.4–2.1) | 2.8 (1.7–8.7)* |
| EXP (ng ml$^{-1}$) | 9.4 (7.5–19 2) | 12.4 (7.8–19.3) |
| MPO (ng ml$^{-1}$) | 188 (105–412) | 740 (352–1405)** |
| PAI-1 (ng ml$^{-1}$) | 1.5 (1.1–5.5) | 1.7 (1.1–6.5) |
| IL-6 (pg ml$^{-1}$) | 0 (0) | 0 (0) |

diluted by 1:5.3. Therefore, the concentrations of histamine, ECP, EPX and MPO detected in FFP may be slightly underestimated compared with donor plasma concentrations.

Concentrations of histamine, ECP, EPX, MPO, PAI-1 and IL-6 in the repeated samples of the 10 u. of fresh plasma and frozen–thawed plasma are shown in table 2. Histamine ($P<0.05$), ECP ($P<0.05$) and MPO ($P<0.01$) concentrations were significantly higher after freezing and thawing compared with fresh plasma before freezing. EPX concentrations were only slightly increased, and PAI-1 concentrations were reduced in all analyses compared with donor plasma concentrations, which in the 24 normal donors were 8.9 (2.6–34.7) ng ml$^{-1}$. IL-6 could not be detected in these samples.

## Discussion

Despite careful donor selection and extensive testing, transfusion of allogenic blood products is associated with adverse reactions, such as immunomodulation,[2] TRALI,[5] ARDS,[6] FNHTR,[3 4] graft-*vs*-host disease (GVHD)[15] and, rarely, transmission of infectious agents.[16] Furthermore, perioperative transfusion with allogenic blood may induce immunosuppression[17 18] which subsequently may increase the risk of developing postoperative infectious complications[2] and increase the risk of recurrence after curative cancer surgery.[2] Hitherto, the mechanisms of these blood transfusion-induced adverse reactions have been poorly understood, but human leucocyte antigen (HLA) expression on donor leucocytes[3] has been suspected to play a role. Consequently, the use of autologous blood has increased, particularly in elective surgery,[19] and it was anticipated to have beneficial effects on blood transfusion-induced infectious complications and on long-term survival. However, results from studies in cancer surgery comparing the effect of allogenic and preoperative donated autologous blood have shown a similar, higher cancer recurrence rate[20] and reduced long-term survival rate[21] in both transfused groups compared with non-transfused patients. Therefore, it was hypothesized that bioactive substances released into the non-cellular component of various transfusion products may play a common role in transfusion-induced adverse effects.[2]

Results from recent studies suggest storage time of blood products plays an important role in the development of adverse reactions[22–24] induced by cytokines[25] and substances with mitogenic activity[22] released into the supernatant. We previously showed storage time-dependent release of histamine, ECP, EPX, MPO and PAI-1 in various erythrocyte suspensions which contain leucocytes and platelets[9 10] while IL-6 was undetectable[10] during storage at +4 °C for 35 days. Results from this study showed that leucocyte non-filtered FFP contained significant amounts of histamine, ECP, EPX and MPO, while IL-6 was not increased compared with control donor plasma concentrations (table 1). In addition, increased concentrations of histamine, ECP and MPO in the 10 u. of thawed FFP compared with samples collected before freezing (table 2) indicated that the substances were released from leucocytes, which are retained in various amounts in plasma during blood component preparation. This assumption is supported by the reduced concentrations of the bioactive substances in pre-storage leucocyte-filtered FFP (table 1). Furthermore, by using sterile microfiltration of plasma from the 10 u. of FFP (table 2) we may have avoided the influence of cellular debris on the analysis of the results. In addition, the low PAI-1 concentration in FFP (table 2) suggests that platelets were retained in the buffy-coat during blood component preparation.

Histamine, ECP, EPX and MPO are preformed and contained in granules in basophils, eosinophils and neutrophils, respectively, while IL-6 is synthesized and released after stimulation[26] and not contained in preformed granules. The freeze–thawing technique used for preparation of FFP at transfusion may lead to total lysis of leucocytes, and simultaneous release of their many bioactive substances into plasma.[9 10] This is supported by detection of leucocytes in fresh plasma[3] while leucocytes are undetectable in thawed FFP.[3]

The clinical impact of these findings is not clear, but as FFP units contain approximately 280 ml of plasma in CPD, the amount of transfused bioactive substances may be significant, at least in massive transfusions, for example to burn trauma patients[27] where accumulation of bioactive substances was related to post-trauma septic reactions.[27] This supports experimental results showing that repeated plasma transfusions are fatal in septicaemic animals.[7] Considerable evidence has emerged to suggest that histamine may have beneficial and detrimental effects on the inflammatory response, immune reaction, coagulation cascade and cardiovascular function.[28–30] ECP and EPX may contribute to immunomodulation, tissue damage and neurotoxicity,[31–34] while MPO may amplify toxic reactions and oxygen free radical-induced tissue damage by hypochlorous acid (HOCl) and N-chloramine (RNHCl) generation.[35–39] Furthermore, some of the substances transfused via FFP are suspected to induce further release of similar and other bioactive substances in the recipient.[40–42] This may support the assumption that bioactive substances in FFP and in other blood products may be detrimental for patients with trauma, septicaemia or undergoing major operations for burn trauma or cardiopulmonary bypass.[2 7 9 43–45]

Although the well known adverse effects of blood component transfusion have been attributed primarily to the presence of contaminating leucocytes, recent data and our data suggest that bioactive substances contained in intracellular granules of leucocytes may play an additional role. Therefore, it should be considered that substances which normally are synthesized and released to protect the host against alloantigen exposure[29 30] occasionally may be detrimental when transfused as part of a massive transfusion regimen. Pre-storage leucocyte filtration should be considered to reduce the content of bioactive substances in FFP, and thereby possibly improve outcome in recipients. The clinical effect of component therapy with exclusively pre-storage leucocyte-filtered blood products compared with conventional prepared products are currently being evaluated in a randomized study of burn trauma patients.

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*British Journal of Anaesthesia* 1997; 78: 553–556

# Responses to simulated anaesthetic emergencies by anaesthetists with different durations of clinical experience

A. J. BYRNE AND J. G. JONES

## Summary

We have compared the responses of four groups of anaesthetists, with different durations of clinical experience, to nine different simulated emergencies. Five anaesthetists in each group completed each of the nine simulated emergencies. Anaesthetists with less than 1 yr experience performed less well than the three other groups of anaesthetists (chi-square, $P<0.02$). However, all groups made serious errors in both diagnosis and treatment, and accepted treatment guidelines were not followed. We have shown that a simple, inexpensive simulator can be used to evaluate the performance of anaesthetists of different durations of clinical experience. (*Br. J. Anaesth.* 1997; **78**: 553–556).

**Key words**
Model, computer simulation. Anaesthesia, audit. Anaesthetists, training.

Errors in the management of emergency situations during anaesthesia are a continuing cause of mortality and morbidity.[1] While both anaesthetic mortality and morbidity are relatively infrequent, the cost in psychological, social and medico-legal terms is considerable. Because these complications are relatively infrequent it is difficult to train anaesthetists to deal with such complications when they occur. Consequently, there is considerable interest in the use of simulators, both in the training of anaesthetists and in the assessment of treatment guidelines.[2–7] Several groups of workers have designed simulators and have investigated their role in education and research.[8–10] While inexpensive computer-based simulators have been criticized for being unrealistic and not testing physical skills, full scale, "high fidelity" simulators, which may cost in excess of £100 000, are likely to be much too expensive to be purchased by individual departments of anaesthesia.

The Anaesthetic Computer Controlled Emergency Situation Simulator (ACCESS)[11] is a "full-scale", "intermediate-fidelity" system and was designed to provide realistic training and a method of assessing performance. Its cost (approximately £3000) is less than many individual pieces of routine anaesthetic monitoring equipment. We have used the simulator to evaluate the performance of anaesthetists with different clinical experience.

## Methods

The ACCESS system consists of a resuscitation manikin representing the patient, a real anaesthetic machine/ventilator and a personal computer which has been programmed to produce a representation of commonly used anaesthetic monitors. The simulations run in real time and are designed to test cognitive and physical skills. Nine different emergencies were presented (table 1).

The simulations were designed to test the most basic anaesthetic skills such as monitoring pulse and ventilation. In addition, the simulated emergencies required the anaesthetist to identify the problem and then to solve it in the same way as during a real emergency, that is by injecting drugs, infusing fluids or altering the settings on the anaesthetic machine.

Each scenario had a predetermined series of therapeutic actions which needed to be taken, but strict adherence to accepted treatment guidelines was not required to cure the "patient". For example, the scenario of anaphylaxis required discontinuation of the anaesthetic and administration of adrenaline and i.v. fluids in appropriate amounts.

We have compared the performance of four groups of anaesthetists with anaesthetic experience allocated to one of four groups: less than 1 yr, between 1 and 2.5 yr, between 2.5 and 5 yr and more than 5 yr. In each experience group, the results for each of five anaesthetists to manage the situation were studied, giving a total of 180 simulations.

All candidates were given a few minutes' explanation before using the simulator but were not allowed any trial runs. The tutor acted as an assistant, passing drugs and equipment, and driving the simulation, but not providing any clues as to the diagnosis or possible treatments. The actions of each anaesthetist were observed and significant actions were timed to the nearest 30 s. The "time to solve" represented the total time for the anaesthetist to identify

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the problem, formulate a solution and perform any necessary actions.

Each simulation was followed through to either patient "recovery" or "death". The times recorded for each scenario are not directly comparable because they represent a range of activities. For example, to cure bradycardia, a single action was required, that is giving a dose of atropine, while in the emergency involving hypotension, the volatile anaesthetic and nitrous oxide had to be discontinued and then fluid administered via the i.v. cannula in the "patient's" arm.

Within each emergency, individual times to successful completion were averaged and SD calculated. Each individual's time was then classified as being either "fast" (less than average for that emergency), "intermediate" (longer than average but not by more than two SD) or "slow" (longer than average plus two SD). Any cases of unsuccessful treatment were also classified as "slow". The statistical significance of the observed differences were assessed using the chi-square test, with Bonferroni correction where appropriate.

## Results

During the study the simulator functioned as expected and all anaesthetists were able to complete their simulations. Responses to 180 emergencies were studied. The emergencies used and the results obtained for each emergency are shown in table 1.

Inadequate treatment leading to the "death" of the "patient" occurred only in the simulation of asystole (10 of 20 simulations), oxygen supply contamination (three of 20), anaphylaxis (five of 20) and failed intubation (14 of 20).

*Table 1* Simulated emergencies, showing the number of "patients" treated inadequately and the average (SD) time to successful treatment. ($n=20$ for each emergency)

| Emergency | Inadequate treatment | Average time (s) |
|---|---|---|
| Bradycardia | 0 | 78.0 (55.6) |
| Hypotension | 0 | 186 (119) |
| Oxygen contamination | 3 | 143 (105) |
| Ventricular tachycardia | 0 | 239 (143) |
| Awareness | 0 | 153 (76.4) |
| Anaphylaxis | 5 | 236 (105) |
| Bronchospasm | 0 | 173 (90.1) |
| Failed intubation | 14 | 220 (87.7) |
| Asystole | 10 | 204 (65.0) |

*Table 2* Simulation emergencies, showing the number of anaesthetists in each group (see text for details) divided into time to treat ($n=20$ for each group)

| Emergency | Fast | Intermediate | Slow |
|---|---|---|---|
| Bradycardia | 12 | 7 | 1 |
| Hypotension | 13 | 6 | 1 |
| Oxygen contamination | 10 | 5 | 5 |
| Ventricular tachycardia | 9 | 11 | 0 |
| Awareness | 13 | 5 | 2 |
| Anaphylaxis | 8 | 6 | 6 |
| Bronchospasm | 11 | 8 | 1 |
| Failed intubation | 3 | 1 | 16 |
| Asystole | 4 | 6 | 10 |

On average, the anaesthetists identified the problem and took appropriate action within 180 s (range 30–570 s). The variation in the time between emergencies reflected both the difficulty in diagnosing the problem and the number of interventions needed to cure the "patient".

Table 2 shows the performance of the anaesthetists during each simulated emergency. As indicated previously, "fast" treatment was considered to be faster than the average for that emergency and "slow" treatment implied either slower than two SD longer than the average time or inadequate treatment.

Figure 1 shows the performance of the four groups of anaesthetists. The most inexperienced group showed fewer "fast" performances and more "slow" performances compared with the three other groups. Overall, the speed of treatment was related to the experience of the anaesthetist ($P<0.02$). When the results of the most inexperienced group were compared with the amalgamated results of the other groups, they were significantly worse ($P<0.02$ with Bonferroni correction).

Although anaesthetists with more than 1 yr experience performed better than inexperienced anaesthetists, they still made serious errors in the treatment of their "patients". For example in the simulation of failure to intubate and ventilate, all anaesthetists eventually resorted to cricothyroid puncture but only six knew how to connect the cannula to a source of oxygen and ventilate the patient's lungs. In the simulations involving cardiac

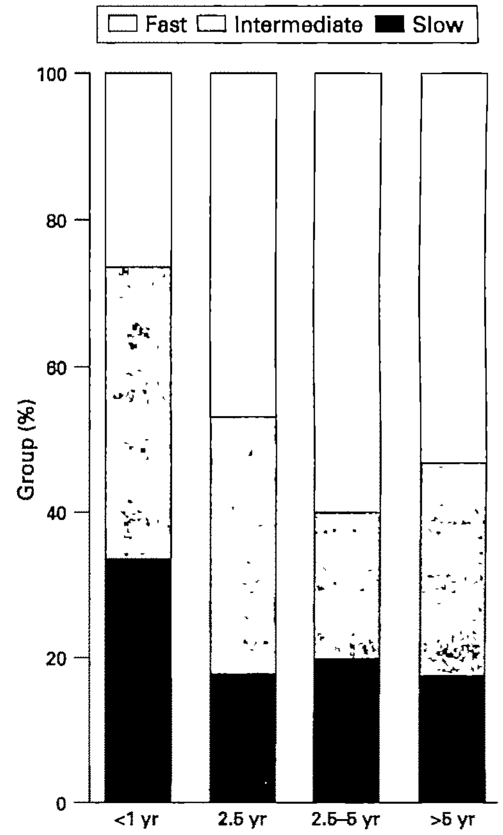

*Figure 1* Percentage of each group of anaesthetists, divided into duration of experience, in each of the three classes of performance. $n=45$ for each group.

arrest or anaphylaxis, no anaesthetist followed the relevant guidelines.

## Discussion

We have demonstrated that the ACCESS simulator can be used to assess the ability of anaesthetists to deal with anaesthetic emergencies. It was able to detect a significant difference in the performance of inexperienced (<1 yr) compared with more experienced anaesthetists. Although a relationship between performance and experience was detected, the results were worrying in that none of the groups of anaesthetists tested, regardless of the duration of training, seemed to be able to deal with all of the simulated emergencies efficiently.

This study can be criticized for not testing anaesthetists during real critical incidents involving real patients. Unfortunately, the rarity of such critical incidents, their inherent variability and their associated medico-legal problems implies that it is practically impossible to study anaesthetists' performances in real-life emergencies. Another criticism is that the simulator is not realistic enough for the results to be used to modify real anaesthetic practice. Editorials published in the anaesthetic literature as far back as 1986[2–7] have commented on the need for new training techniques in anaesthesia and one leading expert in the field has written[4]: "... no industry in which human lives depend on the skilled performance of responsible operators has waited for unequivocal proof of the benefits of simulation before embracing it. In my opinion, neither should anesthesiology". Indeed, in the aviation industry pilots may be exclusively trained and assessed on simulators, so that their first experience of flying the real aeroplane is on a scheduled flight.[12]

The crucial question is whether or not the subjects being tested were able to suspend disbelief. Thus if they are able to react to the simulated events as if they were real, for example saying "Oh no, arterial pressure is falling, can you get me some ephedrine please?", then this is good evidence that disbelief has been suspended. Under these conditions subjects use the same mental models as they use in real life and results are therefore valid.

On the issue of the complexity and realism of the simulator, only six previous articles have described the performance of those tested using time as a criterion.[9 11 13–16] One article described the results from a purely screen-based simulator,[15] while others were based on full-scale, "high fidelity" simulators. The groups included first and second year anaesthetic residents,[9] first and second year anaesthetic residents and experienced practitioners[13] and residents, attendings and anaesthetists in practice.[15]

All of these studies have shown results similar to those produced by ACCESS; performance improved with experience but performance varied greatly, both within and between individuals. When asked to assess the realism of the simulated scenarios on a linear scale of 1 to 10 (10 being totally realistic), in all published evaluations, simulators were rated as between 8 and 8.2,[8 11 17] regardless of whether they were purely computer-based or "full-scale, high fidelity" models. In keeping with the results from ACCESS, the only significant difference in performance was that between the first and second years of training.[9 13] The simplicity of the simulator does not therefore seem to impair the ability to measure performance, which is in keeping with the concept that it is not necessary to construct a "high-fidelity" environment, but merely to provide enough realism to enable those tested to suspend disbelief.

Unfortunately the use of "time to solve" a simulated emergency as a measure of performance may not reflect competence to deal with actual clinical emergencies. For example, in the simulation of bronchospasm it was only the inexperienced anaesthetists who changed the tracheal tube before giving bronchodilators. The more experienced anaesthetists always assumed that the tracheal tube was not the cause of increased airways resistance. This caused some of the less experienced anaesthetists to record a longer "time to solve", but may represent a safer approach. In addition, these results examined only the ability to deal with acute emergencies, they did not test the ability to avoid critical incidents through safe practice.

In addition, classification of anaesthetists by number of years working in anaesthesia does not necessarily take into account seniority. Some of those tested had a considerable number of years of experience, but had not progressed up the career ladder. Although the performance of those anaesthetists might have contributed to the failure of this study to demonstrate a linear relationship between performance and experience, it is important to note that "poor" performances were still recorded by consultant anaesthetists.

Data collected from critical incident studies has been used to validate retrospectively an algorithm for dealing with emergencies.[18] Frequent errors detected during this study suggest that such algorithms may be useful, and simulations promise to provide a way of determining if such algorithms improve performance. Unfortunately, we are not aware that this algorithm has been evaluated prospectively.

In fields other than anaesthesia, simulators have had a marked influence,[19 20] especially in the aviation and nuclear power industries. New theories have been developed to explain the way we identify, classify and react to critical incidents, based on research into human error and the psychology of crisis management. Previously published work using the ACCESS simulator[21] has shown that it can be used to investigate the mental processes anaesthetists use when dealing with emergencies and may allow new error reduction strategies to be developed and evaluated. Further work within the specialty of anaesthesia is needed to determine what the process of "giving an anaesthetic" entails and how the process may be made safer.

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*British Journal of Anaesthesia* 1997; 78: 557–562

# Leakage of fluid past the tracheal tube cuff in a benchtop model

P. J. YOUNG, M. ROLLINSON, G. DOWNWARD AND S. HENDERSON

## Summary

We have assessed a range of high volume, low pressure (HVLP) cuffed tracheal tubes in a benchtop model, for leakage of fluid from above the cuff to the model trachea below, during various ventilatory modes. Rapid leakage occurred in the model during all modes of ventilation, unless tracheal pressure was greater than the height of fluid in the column above the cuff. This leakage occurred preferentially down longitudinal folds that occur in the HVLP cuff wall. This model suggests that, if a longitudinal fold within the cuff wall is patent, then the possibility exists of subglottic to tracheal leakage. (*Br. J. Anaesth.* 1997; **78**: 557–562).

**Key words**
Equipment, tubes tracheal. Model, trachea. Complications, pneumonia. Complications, aspiration. Intubation tracheal.

A tracheal tube with a high volume, low pressure (HVLP) cuff does not protect the lower airway from contamination by material leaking from the subglottis and above, in all circumstances, even with cuff pressure maintained at presently acceptable levels (25–30 cm $H_2O$).[1 2] It has been demonstrated *in vivo*, in patients whose tracheas were intubated with a tube with an HVLP cuff, undergoing general anaesthesia, that leakage occurred in 100% of cases, and this occurred down longitudinal folds within the cuff wall.[3] These folds always occur in an HVLP cuff on inflation within the trachea, as the diameter of the cuff must be greater than that of the trachea for intra-cuff pressure to be equal to tracheal wall pressure. Subclinical leakage of contaminated secretions around the cuff occurs in patients during mechanical ventilation in the intensive care unit (ICU), causing tracheal colonization and increasing the risk of ventilator-associated pneumonia.[4] The objects of this study were to identify the times during standard ventilatory patterns when the dynamic tracheal pressures below the cuff were such that leakage of fluid to the trachea was likely, and to identify aspects of management which are protective against leakage. We have quantified leakage rates in order to demonstrate that macro- (leakage of the order of ml $s^{-1}$) rather than micro-aspiration (leakage of the order of ml $h^{-1}$) can occur along a cuff channel.

## Materials and methods

### LUNG/TRACHEA MODEL

The patient model (fig. 1) consisted of a model lung (Vent Aid, TTL, Michigan Instruments Inc) with a Bear 3 ventilator driving the second mechanically linked bellows (model lung). This was linked to the distal artificial trachea to simulate a lung capable of spontaneous breaths. The artificial trachea was a silicone tube of 2.2 cm internal diameter (Laerdel Medical silicone extension tubing part No 87100) held vertically. The mean diameter of the adult male trachea is 2.2 cm,[5] and a size 8 tracheal tube is used commonly for adult male patients in intensive care practice. The pressure at the distal tip of the tracheal tube was measured via a central venous catheter used as a manometer and introduced through a connector at the proximal end of the tracheal tube. The manometer was filled with saline and transduced (using a Nihon Kohden Lifescope 8) with a saline–air interface. This dynamic pressure was found to be equal to the pressure recorded on a Bicore pulmonary monitor (CP100) placed within the tracheal segment proximal to the water trap.

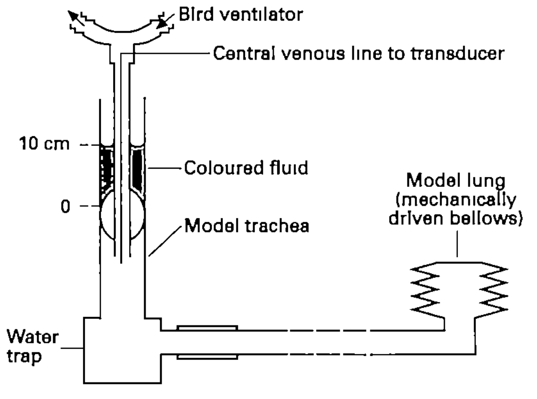
Bird ventilator
Central venous line to transducer
10 cm
0
Coloured fluid
Model trachea
Model lung (mechanically driven bellows)
Water trap

*Figure 1* The mechanical patient model (not to scale).

### EXPERIMENTAL PROCEDURE

The artificial trachea was intubated with a full length (32 cm) size 8 mm internal diameter tube (Portex

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Profile). Intra-cuff pressure was set at 25 cm $H_2O$ manually with a cuff inflator (Monitor control inflator, VBM, Medizintechnik), and was monitored continuously throughout the test. The proximal tracheal tube was connected to a Bird ventilator (6400ST volume ventilator), and continuous positive airway pressure (CPAP) 10 cm $H_2O$ was introduced via the Bird ventilator. When the pressure had stabilized, water coloured with methylene blue was added to the space above the cuff representing the subglottic space and above. The zero point was taken as the top of the cuff in contact with the artificial trachea. A set square and ruler fixed vertically alongside the artificial trachea allowed measurement from the zero point to the lower level of the meniscus. The water was added until a 10 cm head of pressure was achieved. The initial 10 cm $H_2O$ of CPAP was used to hold the fluid in the column above the cuff until the ventilator setting was made, and PEEP/CPAP was adjusted to several different levels (0, 2, 5 and 8 cm $H_2O$) for each ventilatory pattern. One experimenter set the PEEP/CPAP level and an observer blind to this read the level to which the meniscus decreased. The level to which the meniscus decreased was defined as the head of pressure resisted (HPR) for the given ventilatory pattern. All recordings were repeated five times. Inspiratory tidal volume was measured on the Bird internal monitor, and expiratory tidal volume was recorded with a 6800 Bird volume monitor in the expiratory ventilator tubing. Rate of leakage was measured by recording the rate of fall of the meniscus and calculating the volume of fluid lost. A selection of commercially available HVLP cuffed tubes was tested. The vertical model was used as measurement of the fluid column was easier, and water was used to simulate thin secretions.

### MODES EVALUATED

Trough pressure was defined as the minimum pressure recorded from the manometer pressure–time tracing at the tracheal tube tip during the inspiratory phase. In the spontaneous ventilation mode (SV), trough pressure was set by manipulating the driving ventilator (Bear 3) volume–flow settings, until the pressure trace at the distal tracheal tube was found to mimic that in a patient's trachea during SV (unpublished observations in human subjects). This was measured with the same technique during settled ($-2$ cm $H_2O$ trough pressure) and laboured ($-7$ cm $H_2O$ trough pressure) respiration (fig. 2). A spontaneous rate of 20 bpm was set on the driving ventilator. PEEP of 10 $H_2O$ was then introduced before instilling fluid above the cuff.

For the SV+pressure support (PSV) modes, trough pressure was set as above, then a PSV of 7 cm $H_2O$ and trigger sensitivity of 1 cm $H_2O$ were added. HPR during SV, PSV and intermittent positive pressure ventilation (IPPV) modes was recorded 20 min after reduction of CPAP/PEEP to the test level. This time was chosen because the column gradually decreased to an equilibrium level and was static with all ventilatory patterns after 20 min. In the IPPV mode there was no SV, tidal volume was 500 ml, breath rate was 15 bpm, the inspiratory:expiratory ratio was 1:2, and lung compliance was adjusted to create a peak inspiratory pressure at the ventilator of 20 cm $H_2O$.

### CUFFS AND CUFF PRESSURES TESTED

Unless stated otherwise a Portex Profile size 8 tube was used. Comparisons were also made between size 8 models of the Mallinckrodt Hi-Lo, Sheridan HVT, Portex Profile (all inflated to 25 cm $H_2O$) and the Bivona Fome Cuf. The Bivona Fome Cuf is a foam-filled HVLP cuff which is evacuated to allow insertion, and it relies on the distending pressure of the foam to seal the trachea. Rate of leakage was measured with a Portex Profile size 8 tube at intra-cuff pressures of 15, 25 and 60 cm $H_2O$. The effect of CPAP on the rate of leakage was assessed with a Portex Profile size 8 tube at a cuff pressure of 25 cm $H_2O$. HPR was assessed at cuff pressures of 25 and 60 cm $H_2O$ using the Portex Profile size 8 tube.

The effect of tracheal suctioning was also tested (using high suction from a hospital pipeline with a Clement's adapter, which generated a maximum negative pressure of $-400$ mm Hg), with open suction (through a 14CH catheter) and closed suction (Stericath 14F, Portex). The catheter was advanced 5 cm beyond the tracheal tube tip, then withdrawn over a 6-s period under suction. The addition of KY jelly to the cuff was also assessed by liberally coating the cuff with the jelly before intubation of the artificial trachea. The cuff was then tested using the SV, PSV and IPPV ventilatory modes described above, and with peak tracheal pressures of 80 cm $H_2O$ generated using a self-inflating bag (Ambu Resuscitator Mark III). Movement of the KY jelly coated cuff was assessed during IPPV ventilation by displacing the

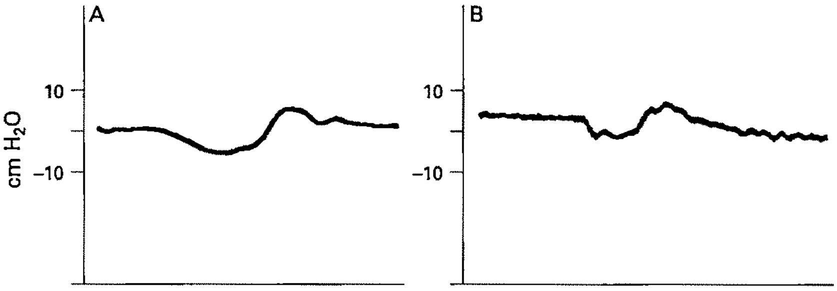

*Figure 2* Pressure profile measured by the central venous catheter with the tip at the distal end of the tracheal tube in (A) a patient and (B) the mechanical model.

tube along 4 cm of the length of the artificial trachea repeatedly (approximately 15 times) over a 6-h period.

STATISTICAL ANALYSIS

Mean and 95% confidence limits for rate of leakage and HPR were calculated (using a Casio scientific calculator), the confidence interval being SEM×1.96.

## Results

HPR remained the same with cuff pressures of 25 cm $H_2O$ compared with 60 cm $H_2O$ (fig. 5), that is 6.42 (6.38–6.46) cm compared with 6.46 (6.29–6.63) cm at 8 cm $H_2O$ of CPAP and 3.52 (3.33–3.71) cm compared with 3.52 (3.41–3.63) cm at 5 cm $H_2O$ of CPAP. However, the rate of flow past the cuff decreased when cuff pressure was increased from 25 to 60 cm $H_2O$, for example with a 3-cm $H_2O$ head of pressure above the cuff, the rate of leakage was 0.27 (0.21–0.33) ml $s^{-1}$ and 0.04 (0.03–0.05) ml $s^{-1}$, respectively (fig. 3).

CPAP and PEEP protected against leakage. Approximately 1 cm head of pressure was resisted for every 1 cm $H_2O$ that CPAP/PEEP was increased (fig. 6). This finding was true for all HVLP cuffs tested. HPR was significantly greater at each level of CPAP for the Mallinckrodt tube, apart from at zero pressure. With a CPAP of 5 cm $H_2O$, HPR for the Mallinckrodt tube was 4.66 (4.47–4.85) cm $H_2O$, significantly higher than HPR for the Portex tube (3.52 (3.33–3.71) cm $H_2O$). More negative trough pressures during spontaneous ventilation reduced HPR at all CPAP levels. With a CPAP of 5 cm $H_2O$, a decrease in trough pressure from −2 to −7 cm $H_2O$ reduced HPR from 3.22 (3.05–3.39) cm $H_2O$ to 2.08 (1.98–2.18) cm $H_2O$ (fig. 7). PSV of 7 cm $H_2O$ increased HPR to 5.56 (5.46–5.66) cm $H_2O$ and 3.52 (3.22–3.82) cm $H_2O$, respectively (fig. 8).

IPPV had a protective effect equivalent to approximately 1.5–2.5 cm $H_2O$ of PEEP/CPAP, for

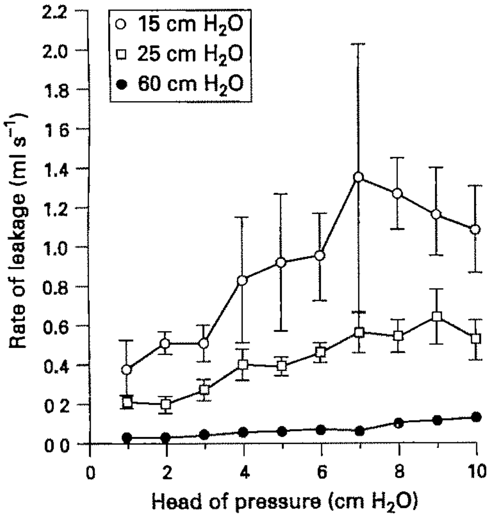

*Figure 3* Effect of cuff pressure (15, 25 and 60 cm $H_2O$) on rate of leakage of water past a Portex Profile size 8 tracheal tube (mean, 95% confidence intervals).

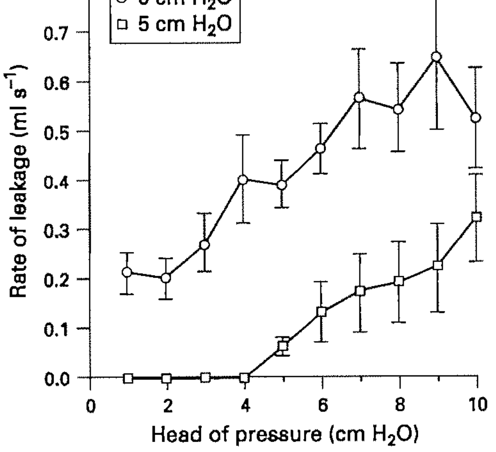

*Figure 4* Effect of CPAP 5 cm $H_2O$ on the rate of leakage of water past a Portex Profile size 8 tracheal tube at a cuff pressure of 25 cm $H_2O$ (mean, 95% confidence intervals).

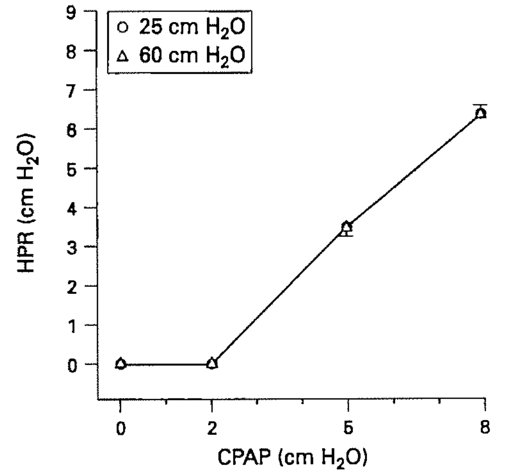

*Figure 5* Effect of cuff pressure (25 and 60 cm $H_2O$) on the head of pressure resisted (HPR) at various CPAP levels using a Portex Profile size 8 tracheal tube (mean, 95% confidence intervals).

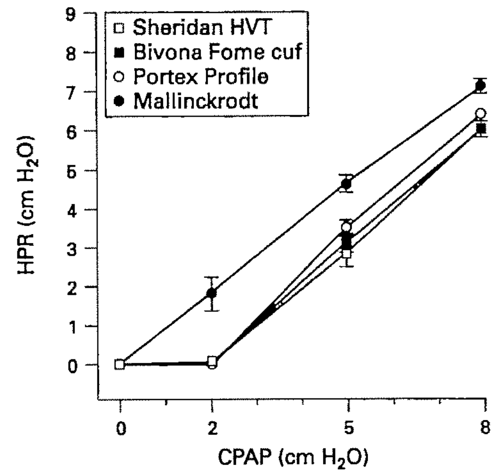

*Figure 6* Effect of cuff brand on the head of pressure resisted (HPR) at various CPAP levels using size 8 tracheal tubes (Sheridan HVT, Portex Profile and Mallinckrodt Hi-Lo at 25 cm $H_2O$, and the Bivona Fome Cuf) (mean, 95% confidence intervals).

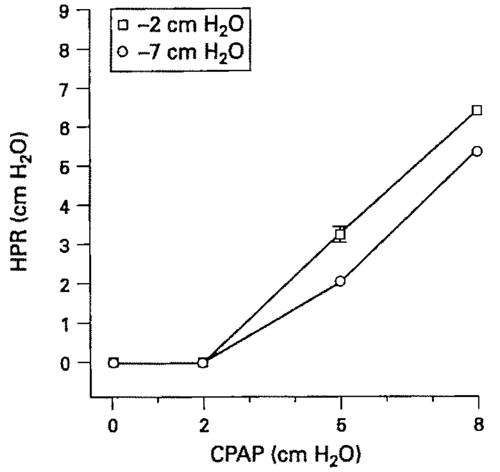

*Figure 7* Effect of spontaneous respiratory efforts on the head of pressure resisted (HPR) during simulated quiet respiration (inspiratory trough pressure of −2 cm $H_2O$) and simulated agitated respiration (inspiratory trough pressure of −7cm $H_2O$) at various CPAP levels using a Portex Profile size 8 tracheal tube at 25 cm $H_2O$ (mean, 95% confidence intervals).

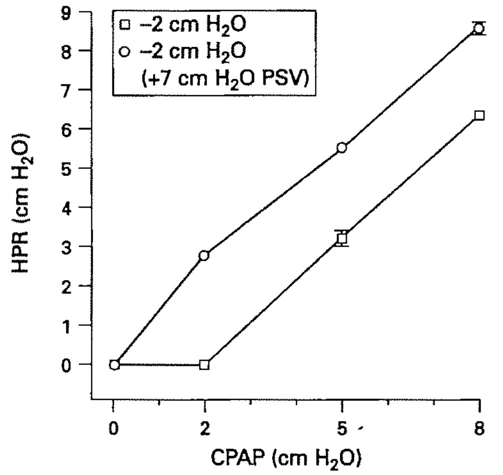

*Figure 8* Effect of pressure support ventilation (PSV) on the head of pressure resisted (HPR) during simulated quiet respiration (inspiratory trough pressure of −2 cm $H_2O$), at various CPAP levels using a Portex Profile size 8 tracheal tube at 25 cm $H_2O$ of cuff pressure (mean, 95% confidence intervals).

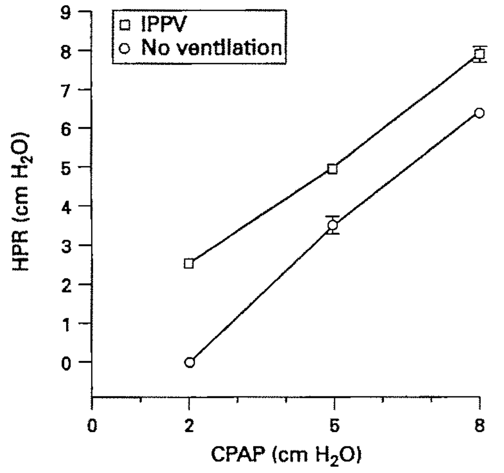

*Figure 9* Effect of intermittent positive pressure ventilation (IPPV) on the head of pressure resisted (HPR) at various CPAP levels using a Portex Profile size 8 tracheal tube at 25 cm $H_2O$ of cuff pressure (mean, 95% confidence intervals).

example at 5 cm $H_2O$ of CPAP/PEEP, IPPV increased HPR from 3.52 (3.33–3.71) cm $H_2O$, with no ventilation but constant CPAP, to 4.94 (4.82–5.06) cm $H_2O$ (fig. 9).

Neither open nor closed tracheal suctioning protected against generation of large negative tracheal pressures (less than −40 cm $H_2O$) or leakage of fluid in this model. Movement of the tube within the trachea caused minimal leakage. Loss of cuff pressure (to 15 cm $H_2O$) caused rapid leakage independent of CPAP. On deflation of the cuff, however, it was possible to expel some of the fluid out of the model, particularly at higher CPAP/PEEP levels (e.g. 15 cm $H_2O$). It was possible to ventilate the model for 24 h with no leakage (for example with an SV rate of 15 bpm, trough pressure −2 cm $H_2O$, PSV 7 cm $H_2O$ and PEEP 5 cm $H_2O$, and 4 cm of fluid above the cuff). After this period of no leakage, the tracheal tube was disconnected as is our practice for tracheal suctioning. At disconnection rapid leakage of fluid to the trachea occurred; this was increased with suctioning. Application of KY jelly to the cuff before intubation protected against leakage during all ventilatory modes studied. Application of high airway pressures during bagging, or movement of the tube over time, allowed a jelly filled channel to open, and leakage to occur. When a channel had cleared of jelly the leakage persisted over time.

## Discussion

This model of an intubated trachea did not attempt to simulate the surface of contact between the tracheal mucosa and the cuff, the static or dynamic properties of the tracheal and extra-tracheal tissues during ventilation, the properties of different consistencies of secretions or the effect of mucus on the cuff–tracheal interface. Fluids of different viscosities were not assessed and it is possible that rate of leakage would be reduced and HPR increased with viscous secretions. Within the confines of a benchtop model, this study suggests aspects of ventilatory management which are protective against leakage and aspects which make leakage more likely.

Leakage occurs down longitudinal folds within the cuff walls, and these folds formed in all HVLP cuffs tested. Testing different tubes showed that HVLP cuffs of a range of specifications all behaved similarly regarding leakage, the Mallinckrodt tube having a marginally but significantly higher HPR when CPAP/PEEP levels were greater than zero. This protective effect of the Mallinckrodt tube might be beneficial when the subglottic space is suctioned mechanically to reduce secretions above the cuff. Indeed, the rate of ventilator-associated pneumonia can be reduced with the use of mechanical subglottic secretion drainage and this cuff (Mallinckrodt Hi-Lo EVAC tube).[6]

Several factors increasing the possibility of leakage were identified. Tracheal suctioning through a 14CH catheter caused tracheal pressures to decrease to less than −40 cm $H_2O$ and caused rapid leakage. Increasing cuff pressure from 25 to 60 cm $H_2O$ decreased the rate of flow past the cuff, but did not increase HPR, so the column of fluid decreased to the same level ultimately, although it took longer to do so. Clinically, this exerts unacceptable pressures on the tracheal wall,[2] but it might be acceptable to increase cuff pressure for brief periods during times when the risk of leakage is greatest. A decrease in cuff pressure to 15 cm $H_2O$ caused rapid leakage; this can occur clinically with a leak from the cuff or pilot balloon, a change in tracheal compliance or a change in position or angle of the cuff within the trachea. The high variability of the data for flows at a cuff pressure of 15 cm $H_2O$ may have been caused by errors in measuring short time intervals, with high flows, using a stopwatch.

Aspects protective against leakage are those that increase the pressure head of fluid resisted above the cuff. CPAP and PEEP were protective (approximately 1 cm head of pressure was resisted for every 1 cm $H_2O$ of CPAP/PEEP for all cuffs), as was expected. This held for all HVLP cuffs tested, the Mallinckrodt cuff performing modestly better for a given CPAP level. If fluid builds up to above the level of CPAP/PEEP, then leakage occurs on a millilitre-for-millilitre basis as fluid is formed, provided the obligatory fold in the cuff is patent and not occluded with KY jelly or viscous secretions.

Application of KY jelly to the cuff before intubation was protective against leakage until an air leak developed. This air leak was small and not detectable on the inspiratory–expiratory tidal volume monitors. This suggests that the temporary plugging of the cuff channels by application of jelly before intubation could be beneficial in the short term.

More negative trough pressures ($-7$ cm $H_2O$) during spontaneous ventilation, representing laboured respiration (for example during testing for response to painful stimuli in an obtunded patient), reduced HPR at all CPAP levels and were therefore more likely to produce leakage. PSV protected against leakage during spontaneous respiration.

The protective effect of IPPV was equivalent to only a few centimetres of PEEP. HPR in the trough pressure of $-2$ cm $H_2O$+PSV group was higher than that of the IPPV group, which was higher than the no ventilation group for a given CPAP/PEEP. The reason for this might be because of a shorter expiratory phase in the $-2$ cm $H_2O$ trough pressure+PSV group than in the IPPV group, or the nature of the cyclical cuff compression with each ventilatory waveform.

The time (20 min) allowed for equilibrium in the ventilated groups was necessary because of the nature of the leak in the period before equilibrium was reached. A column of fluid would form in a fold, and a drop would drip into the distal model trachea initially with every ventilator cycle, then as the level approached equilibrium a drip would occur with increasingly less frequent cycles. Between each of these cycles the column within the fold would be expelled proximally with each increase of airway pressure, and form again when the distal tracheal pressure decreased. No further drops fell after a 20-min period.

Movement of the cuff within the trachea caused minimal leakage, but loss of cuff pressure (to 15 cm $H_2O$) caused rapid leakage independent of CPAP. It was possible, however, to expel some of the fluid out of the model, particularly at higher PEEP levels (e.g. 15 cm $H_2O$); this represents the clinical practice of those who apply PEEP or a large tidal volume on deflating the cuff at extubation.

In patients undergoing ventilation in the ICU with tracheal colonization, 85% were found to have identical microorganisms on both sides of the cuff.[6] It is likely that many cases of ventilator-associated pneumonia are a result of this route of contamination.[7] In ICU patients, up to 150 ml per day can be removed from the subglottic space by intermittent aspiration using a Hi-Lo EVAC tube (Mallinckrodt),[6] and in our experience with a patient prone, over 50 ml per hour at times could be collected dripping from the nose and mouth (unpublished observations). In supine or semi-recumbent patients, secretions do not overflow from the mouth, but pool in the oropharynx. When a pool has collected, further secretion production is presumably either inhibited, reabsorbed through oropharyngeal mucosa or drains into either the stomach or past the tracheal cuff. In this model, if fluid is added continually above the cuff, it continues to drain to the model trachea at the same rate, maintaining a constant pool above the cuff equal to the head of pressure resisted for that ventilatory pattern.

If this model represents the clinical situation then there are readily identifiable times when a patient with an intubated trachea aspirates subglottic fluid to the trachea, and manoeuvres that protect against this. Manoeuvres to reduce pressure differentials across the cuff, such as large tracheal tube diameters, better demand valves to avoid decreases in airway pressure and CPAP/PEEP would increase protection against leakage of subglottic fluid. This pool, however, would be available for leakage at any time during routine care when this protection was lost.

In summary, in an intubated model trachea, when a patent longitudinal fold exists in the HVLP cuff, there are identifiable times when gross leakage past the cuff occurs. This happens when the pressure difference across the cuff is favourable for flow to the trachea. Such clinical situations would be: (1) tracheal suctioning with 14CH catheters, either open or closed; (2) loss of cuff pressure; (3) loss of PEEP/CPAP such as disconnection from the ventilator; (4) continuing secretion production when the maximal protective effect of the particular ventilatory pattern has been reached; and (5) negative tracheal inspiratory pressures.

The possibility of leakage in this model is reduced when the pressure difference across the cuff favours flow from the trachea or the channels are blocked. This would occur with: (1) Trendelenburg position or subglottic aspiration before disconnection, extubation or suctioning the trachea; (2) maintaining CPAP/PEEP in the trachea, at all times; (3) use of PSV/IPPV and not allowing SV through a tube without support; (4) KY jelly lubrication on intubation; and (5) reduction in the subglottic and pharyngeal pool.

A new design of cuff in which folds are not present and wall pressure is maintained at acceptable levels would offer advantages. If such a cuff could be maintained at a tracheal wall pressure of 30 cm $H_2O$ reliably, then the barrier to fluid flow past the cuff would be at least equal to a HPR of 30 cm $H_2O$, and would withstand at least negative 30 cm $H_2O$ tracheal pressures. This would prevent leakage under most clinical circumstances. There is a need for the development of a tracheal tube cuff which protects against leakage, while exerting acceptable pressures on the tracheal wall.

## Acknowledgements

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# 5-HT spinal antinociception involves mu opioid receptors: cross tolerance and antagonist studies

C. S. Goodchild, Z. Guo, J. Freeman and J. P. Gent

**Summary**

The antinociceptive effects of intrathecal 5-HT, fentanyl, ICI197067 and U50488H were assessed by electrical current nociceptive threshold and tail flick latency measurements. Equieffective doses of these agonists were then given intrathecally with a range of doses of naloxone or the highly selective μ opioid antagonist, β-funaltrexamine. Antagonist dose–response curves were plotted. Other rats were made tolerant to either fentanyl or 5-HT by intrathecal injections of these drugs seven times daily and the antinociceptive effects of intrathecal fentanyl and 5-HT were assessed in each group. All intrathecal drugs caused spinally mediated antinociception in both tests. The antinociceptive effects of intrathecal 5-HT assessed by the electrical test (ECT) but not by tail flick latency (TFL) were suppressed by both opioid antagonists at doses similar to those required to suppress all of the effects of intrathecal fentanyl. The ED$_{50}$ values were 0.22 (fentanyl, ECT), 0.25 (fentanyl, TFL) and 0.18 (5-HT, ECT) μmol kg$^{-1}$ for naloxone and for β-funaltrexamine 2.2 fmol (5-HT, ECT), the same order as that required to produce similar suppression of the antinociceptive effects of fentanyl (46 amol: fentanyl, ECT; 4.6 fmol: fentanyl, TFL) and very different from the ED$_{50}$ for β-FNA suppression of the antinociceptive effects of the kappa opioid, U50488H (5.88 pmol). Cross tolerance in both directions was demonstrated between intrathecal fentanyl and 5-HT in the electrical test but not in the tail flick test. We conclude that intrathecal 5-HT caused spinally mediated antinociceptive effects revealed by electrical current and tail flick latency tests. The antinociceptive effects in the electrical test involved spinal cord μ opioid receptors. (*Br. J. Anaesth.* 1997; **78**: 563–569).

**Key words**

Pain, experimental. Pain, mechanisms. Pain, threshold. Serotonin (5-hydroxytryptamine). Antagonists opioid.

The antinociceptive effects of spinally administered 5-hydroxytryptamine (5-HT) are well established.[1–3] Spinal 5-HT probably mimics the activity of 5-HT containing fibres descending from neurones located in the brainstem raphe nuclei, electrical stimulation of which also produces antinociceptive effects in awake animals[4] and inhibition of responses to noxious stimulation of the skin in single dorsal horn neurones.[5] The 5-HT antagonist methysergide has been shown to reverse the antinociception produced by spinal 5-HT in addition to producing hyperalgesia in rats when used intrathecally alone.[3 6–11] These latter experiments imply that 5-HT receptors are involved in spinal antinociception.

Some electrophysiological studies have also suggested that opioid systems might be involved with these effects. Oliveras and colleagues[12 13] reported that electrical stimulation of the raphe nuclei could produce powerful antinociceptive effects in tests using noxious pinch and threshold of the jaw opening reflex in the cat and that naloxone could also completely abolish this antinociceptive effect in 12 of 16 cases. Similar observations were made by Akil, Mayer and Liebeskind[14] who, using tail flick latency measurements, found that antinociceptive effects caused by electrical stimulation of the periaqueductal grey matter in the rat could be partially reversed by the same opioid antagonist. The site of this opioid–serotonergic interaction (spinal cord or brain site) is uncertain and the interaction is also controversial as other groups have failed to confirm these results.[15 16]

The purpose of this study was first to confirm the involvement of opioid systems in 5-HT antinociception. Measurement of tail flick latency (TFL) and electrical current threshold (ECT) for nociception were the tests used. With this combination it is possible to demonstrate segmental or differential antinociceptive effects of intrathecally administered drugs thus proving that the action of the drug is confined to the caudal segments of the spinal cord responsible for tail innervation. This is achieved by showing increases in ECT in the tail after intrathecal drug administration without any change in the neck and it is possible to demonstrate simultaneously the effects of the drug on TFL.[17] We have investigated the actions of two opioid antagonists, naloxone and β-funaltrexamine, on spinally

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mediated antinociceptive effects after intrathecal injection of 5-HT and selective opioid receptor agonists. This was followed by study of the occurrence of tolerance and cross tolerance between intrathecally administered 5-HT and fentanyl.

## Materials and methods

This work was carried out with permission of the licensing authorities of the UK (Home Office Licence PPL50/00131). In all experiments attention was paid to ethical guidelines for investigation of experimental pain in conscious animals.[18] Experiments were performed on 86 male Wistar rats (weight 150–200 g) with chronically implanted subarachnoid catheters, as described previously.[17] Measurement of ECT for nociception and TFL were used to demonstrate spinally mediated antinociceptive effects of intrathecally administered 5-HT, fentanyl ($\mu$ opioid agonist; Sublimaze; Janssen Pharmaceutical), ICI197067 and U-50488H ($\kappa$ opioid agonists; Sigma, London; Semat Technical Ltd, St Albans, UK). The conduct of the nociceptive tests and use of lignocaine (10 $\mu$l; 2%) to prove the intrathecal position of the catheter were as described in previous publications.[17 19 20] The responses to the drugs were standardized by expressing the threshold current as a ratio of the control (pre-drug) value as in previous studies, and TFL as a percentage maximum possible effect (% MPE) as follows[17 19 20]:

$$\%\,\text{MPE}=\frac{\text{mean TFL (post-drug)}-\text{mean TFL (pre-drug)}}{\text{cut-off time (10 s)}-\text{mean TFL (pre-drug)}}$$

### 5-HT DOSE–RESPONSE RELATIONSHIP

ECT measurements were made in the tail and neck in 54 experiments in which a range of doses of intrathecal 5-HT was administered (0.24–2.36 $\mu$mol; 50–500 $\mu$g). These data were used to establish the dose–response relationship for 5-HT in the ECT test. TFL was also measured in 28 of these experiments after intrathecal 5-HT (0.24–1.89 $\mu$mol; 50–400 $\mu$g). These measurements were used to establish the dose–response relationship for 5-HT in the TFL test. In 15 of the experiments the time course of the antinociceptive effects of 5-HT (300 $\mu$g; 1.41 $\mu$mol) was calculated as described previously.[17]

Data from this dose–response relationship and from previously published dose–response curves were used to choose the doses of agonists to be used in subsequent experiments; doses that were approximately equipotent and towards the top of the dose–response curve.[17 21 22] Thus the doses of intrathecal agonists used in subsequent experiments were: 5-HT 1.89 $\mu$mol; fentanyl 0.74 nmol; ICI 197067 1.5 nmol; U50488H 210 nmol.

### EXPERIMENTS WITH NALOXONE

To investigate the effects of naloxone on different agonists, experiments were performed with intrathecal 5-HT 1.89 $\mu$mol ($n$=58), fentanyl 0.74 nmol ($n$=30) and intrathecal ICI 197067 1.5 nmol ($n$=18). ECT and TFL measurements were made. The agonists were given intrathecally alone before and after a series of intervening experiments in which the same dose of intrathecal agonist was given after i.p. injection of naloxone (0.02–5.5 $\mu$mol kg$^{-1}$; 0.0075–2 mg kg$^{-1}$; dissolved in 1 ml of physiological saline). Percentage suppression of agonist effect by each dose of naloxone was calculated by the following expression:

$$\%\ \text{suppression}=\frac{R-r}{R-1}\times 100$$

where $R$=mean effect of agonist alone and $r$=effect of agonist in the presence of naloxone. Values for each dose of antagonist were combined to produce means (SEM) and plotted to produce naloxone dose–response curves as described previously.[22]

### EXPERIMENTS WITH $\beta$-FUNALTREXAMINE

A similar series of experiments was performed with the highly selective $\mu$ opioid antagonist, $\beta$-funaltrexamine $\beta$-FNA (Semat, St Albans, UK) in the dose range $10^{-18}$–$10^{-10}$ mol intrathecally[23–26] using 5-HT 1.89 $\mu$mol, fentanyl 0.74 nmol and U-50488H 210 nmol ($\kappa$-selective opioid) as intrathecal agonists. In each rat only one experiment was carried out for measurement of the antinociceptive effects of the agonist given alone and one (24 h later) for the effects of agonist with antagonist because of the irreversible nature of the block caused by $\beta$-FNA at $\mu$ opioid receptors.[24] Percentage suppression of the antinociceptive effects of each agonist by $\beta$-FNA was calculated as described above for naloxone, and $\beta$-FNA dose–response curves were plotted.

### CONTROLS

Five experiments were performed in which the effects of i.p. naloxone given alone (5.5 $\mu$mol kg$^{-1}$; 2.0 mg kg$^{-1}$; dissolved in 1 ml of physiological saline) were assessed in both the ECT and TFL tests. In another group, five rats with intrathecal catheters were given intrathecal $\beta$-FNA $10^{-10}$ mol alone and the effects assessed in both tests (ECT and TFL). These were the highest doses of antagonists used.

### TOLERANCE STUDIES

Forty-two rats with lumbar subarachnoid catheters were allocated to one of four groups. On the day after intrathecal cannulation the effect of intrathecal 5-HT 1.89 $\mu$mol on ECT and TFL were measured in groups 1 and 3, and the effect of intrathecal fentanyl 0.74 nmol on ECT and TFL was assessed in groups 2 and 4. On the next day, the effect of the same dose of fentanyl on ECT and TFL was measured in groups 1 and 3 and the effect of the same dose of 5-HT was measured in both tests in groups 2 and 4. For the next 3 days, the rats were treated as follows: (1) on each day, the 5-HT group ($n$=16) received seven intrathecal injections of 5-HT 1.89 μmol at hourly intervals; the effects of 5-HT on ECT and TFL were measured for the first of these injections each day; (2) on each day, the fentanyl group (*n*=16) received seven intrathecal injections of fentanyl 0.74 nmol at hourly intervals; the effects of fentanyl on ECT and TFL were measured for the first of these injections each day; (3) on each day, the control group of rats (*n*=5) received seven doses of 0.9% saline 5 μl (the vehicle for both drugs) intrathecally at hourly intervals and the effects of intrathecal 5-HT 1.89 μmol on ECT and TFL were measured once at the beginning of each day; (4) on each day, another control group of rats (*n*=5) received seven intrathecal injections of 0.9% saline 5 μl at hourly intervals and ECT and TFL responses were tested once at the beginning of each day with intrathecal fentanyl 0.74 nmol.

Thus in groups 1 and 2 attempts were made to induce tolerance to either 5-HT (1) or fentanyl (2). Groups 3 and 4 acted as controls receiving only saline intrathecal injections, except for one dose of agonist each day (5-HT, group 3; fentanyl, group 4) to assess the effects of the agonist in the ECT and TFL tests without frequent repeated dosing.

On the sixth day after cannulation the responses to 5-HT and fentanyl were measured again using both nociceptive tests so that they could be compared with the effects of both drugs on ECT and TFL measured on days 1 and 2 after cannulation. Thus changes in the effects of fentanyl in both nociceptive tests could be examined in animals made tolerant to 5-HT by repeated injections of this drug and vice versa for changes in 5-HT effects in fentanyl tolerant animals.

## Results

Intrathecal injection of 5-HT caused increases in ECT in the tail without any change in ECT in the neck (differential responses). These differential responses were used in the calculation of dose–response relationships.

### INTRATHECAL 5-HT DOSE–RESPONSE RELATIONSHIP

Figure 1 shows the dose–response relationship for intrathecal 5-HT in both nociceptive tests. Intrathecal 5-HT caused dose-related antinociceptive effects assessed by both tests. The dose of 0.9 μmol was the lowest dose which produced significant antinociceptive effects in the TFL test ($P$=0.0064; paired Student's *t* test) and in the ECT test ($P$=0.0046; paired Student's *t* test). Doses of 1.89 μmol and 2.36 μmol caused maximum antinociceptive effects in the TFL and ECT tests, respectively. Both doses caused differential responses.

Figure 2 shows the time course of the antinociceptive effects of intrathecal 5-HT 1.4 μmol assessed with the ECT and TFL tests. 5-HT caused significant increases in ECT in the tail with no change in ECT in the neck. There was also a simultaneous increase in TFL which lasted, as with the ECT change, for 20 min after intrathecal injection.

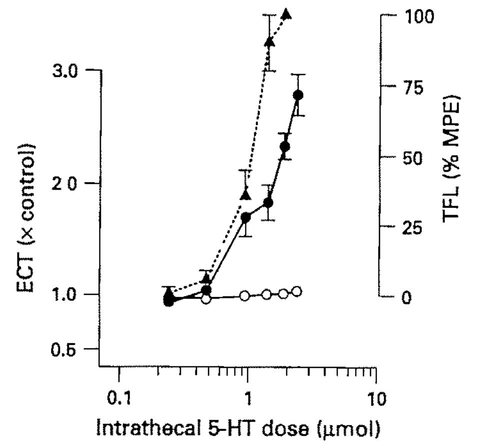

*Figure 1* Dose–response relationship for intrathecal 5-HT. Nociceptive thresholds were measured with increasing doses of intrathecal 5-HT (0.024–2.36 μmol) using the ECT (tail and neck) and TFL tests. Nociceptive thresholds were measured every 5 min for 15 min before and 30 min after intrathecal 5-HT. Responses for TFL measurements were expressed as percentage maximum possible effect (% MPE) and the increases in ECT values were expressed as a ratio of control (pre-drug) values for each set of electrodes. Values were grouped for each drug dose and are shown as mean, SEM (*n*=6–10). ▲=TFL; ●=ECT (tail); ○=ECT (neck).

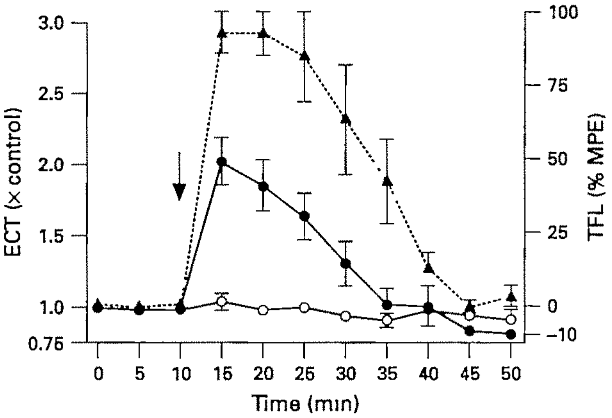

*Figure 2* Time response relationships for intrathecal 5-HT in the ECT and TFL tests. Each rat was given the same dose of intrathecal 5-HT 1.41 μmol (arrow). Each value of ECT (neck and tail) and TFL was standardized by dividing that value by the mean of the three values for that test at that site (neck or tail) taken before drug administration. These calculated values were then combined for each time and shown on the graph as mean, SEM (*n*=9). After injection of 5-HT (arrow) the antinociceptive effects occurred with both tests within 5 min and remained significantly above baseline for another 15–20 min ($P$<0.01, paired *t* test). ▲=TFL; ●=ECT (tail); ○=ECT (neck).

### EXPERIMENTS WITH NALOXONE

Naloxone i.p. caused dose-related suppression of the antinociceptive effects of fentanyl assessed in both the ECT and TFL tests (fig. 3). Naloxone i.p. also suppressed the antinociceptive effect of intrathecal 5-HT assessed by the ECT test. However, the antinociceptive effect of intrathecal 5-HT assessed by the TFL test was not affected by i.p. naloxone (fig. 3) although TFL measurements were made in the same experiments as those showing dose-related suppression of the increase in ECT. The values contributing to each curve were entered into a computer program (Statistica for Windows v 4.5) and doses

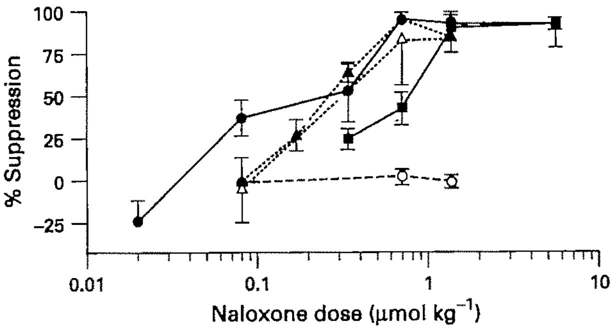

*Figure 3* Naloxone dose–response curves for suppression of the spinally mediated antinociceptive effects of intrathecal injections of fentanyl 0.74 nmol, ICI 197067 1.5 nmol and 5-HT 1.89 μmol. These doses of intrathecal agonist were equipotent in producing spinally mediated antinociception in the ECT test. They were given alone to establish a control response and then at the same time with a range of doses of naloxone i.p. The resulting reduction in response to the agonist in the ECT and TFL tests were calculated as percentage suppression of the response to agonist alone. Results for each dose of antagonist against each agonist were combined to produce mean, SEM ($n$=4–10). Naloxone caused dose-related suppression of 5-HT effects on ECT and all the antinociceptive effects of the opioids. Naloxone caused no suppression of 5-HT effects assessed by TFL. Higher doses of naloxone were needed to cause suppression of ICI 197067 antinociception compared with 5-HT and fentanyl, which were similar to each other. ●=5-HT ECT; O=5-HT TFL; ▲=fentanyl ECT; Δ=fentanyl TFL; ■=ICI197067.

were calculated that would produce 50% suppression of each agonist response (ED$_{50}$). These values were 0.22 (fentanyl, ECT), 0.25 (fentanyl, TFL) and 0.18 (5-HT, ECT) μmol kg$^{-1}$. Thus the ED$_{50}$ for i.p. naloxone that would cause 50% suppression of the antinociceptive effects of fentanyl assessed by both tests was similar to that causing 50% suppression of the effects of 5-HT in the ECT test. This is also the same value that was obtained previously in the same preparation[22] and it was much less than the dose of naloxone required to produce 50% suppression of κ opioid spinally mediated antinociception (the ED$_{50}$ for naloxone suppression of ICI 197067 was 0.64 μmol kg$^{-1}$, calculated with Statistica for Windows v 4.5) (fig. 3).

### EXPERIMENTS WITH β-FUNALTREXAMINE

β-FNA selectively antagonized the antinociceptive effects of the μ opioid fentanyl (fig. 4). Intrathecal β-FNA also caused dose-related suppression of the antinociceptive effect of 5-HT assessed by the ECT test but it did not cause any significant attenuation of the effect of intrathecal 5-HT on TFL measured in the same experiments. The ED$_{50}$ of β-FNA for suppression of the effects of 5-HT (ECT) was 2.2 fmol and of the same order as that required to produce similar suppression of the antinociceptive effects of fentanyl (46 amol: fentanyl, ECT; 4.6 fmol: fentanyl, TFL) and very different from the ED$_{50}$ for β-FNA suppression of the antinociceptive effects of the kappa opioid U50488H (5.88 pmol) (Statistica for Windows v 4.5).

The dose of U-50488H (210 nmol) used in these experiments caused a significant increase in tail ECT values (mean 1.71 (SEM 0.08), $P<0.05$) with no changes in neck ECT values; this increase was significantly less than the increases in tail ECT caused by the other drugs (2.35 (0.13), 5-HT; 2.1 (0.1), fentanyl; 2.3 (0.22), ICI197067) which were equieffective ($P>0.05$ unpaired *t* test). Although the dose of U-50488H was less efficacious than the other agonists, β-FNA only caused dose-related suppression of the antinociceptive effects of U-50488H at much higher doses of the antagonist than those effective at suppression of the effects of fentanyl and 5-HT (ECT).

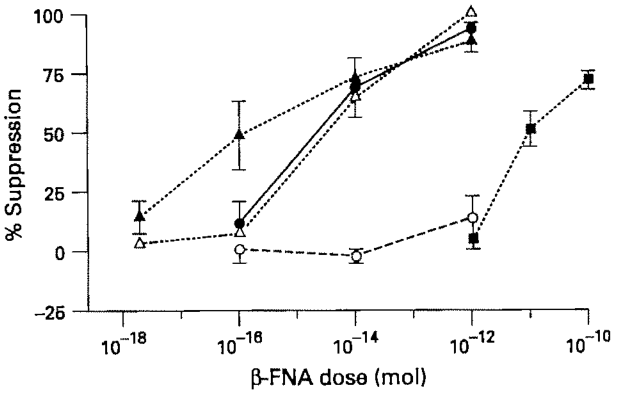

*Figure 4* Beta-funaltrexamine (β-FNA) dose–response curves for suppression of spinally mediated antinociceptive effects of intrathecal injections of fentanyl 0.74 nmol, U-50488H 210 nmol and 5-HT 1.89 μmol. These equipotent doses of intrathecal agonist were first given alone and in subsequent experiments mixed with the antagonist β-FNA. The response to the agonist was calculated as percentage suppression of the control agonist response and the values calculated for each dose of antagonist were combined to produce mean, SEM ($n$=5). The dose–response relationship for suppression of fentanyl TFL and ECT effects was similar to that for suppression of 5-HT effects assessed by the ECT test. There was no suppression of the TFL effects of intrathecal 5-HT even in those experiments in which doses of β-FNA were used that were sufficient to cause >90% suppression of the ECT response. Much higher doses of β-FNA were needed to suppress the effects of the κ-selective opioid agonist U-50488H. ●=5-HT ECT; O=5-HT TFL; ▲=fentanyl ECT; Δ=fentanyl TFL; ■=U50488H.

### TOLERANCE STUDIES

Figure 5A shows the development of tolerance to 5-HT in 5-HT-treated animals (group 1) compared with saline-treated animals (group 3). The response to intrathecal 5-HT (350 μg; 1.89 μmol) in the ECT test was reduced significantly in animals in group 1 after the first day's treatment of seven intrathecal injections of 5-HT 1.89 μmol ($P<0.0001$; paired *t* test). The response assessed by the TFL test, in the same group of animals with the same dose of 5-HT (fig. 5B), was reduced but was not significantly different from control. After the second day's treatment the response in the TFL test was significantly lower than that in the control measured in those rats on day 1 ($P=0.0358$; paired *t* test). However, these statistically significant differences for TFL measurements were not supported by comparison with *saline-treated* control animals ($P>0.05$; unpaired *t* test); this comparison did not support the occurrence of tolerance to intrathecal 5-HT in the TFL test. In contrast, it revealed highly statistically significant ($P<0.001$) diminution in responses to

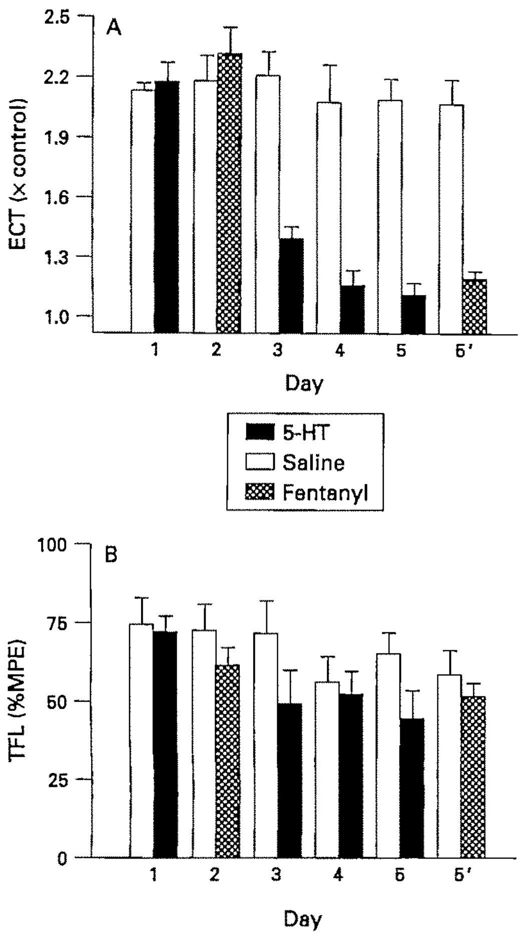

*Figure 5* Tolerance to intrathecal 5-HT. A: ECT responses in rats treated with intrathecal injections of 5-HT six times daily and saline. Responses on days 1, 3, 4 and 5 were measured at the beginning of the day to a single dose of 5-HT 1.89 μmol. The cross-hatched bars denote responses on days 2 and 5 (end of day 5 (5′)) to intrathecal fentanyl 0.74 nmol. B: The same procedure with 5-HT and fentanyl but results shown are for the TFL test. Results are mean, SEM ($n$=5 for saline-treated rats and $n$=10 for drug-treated rats).

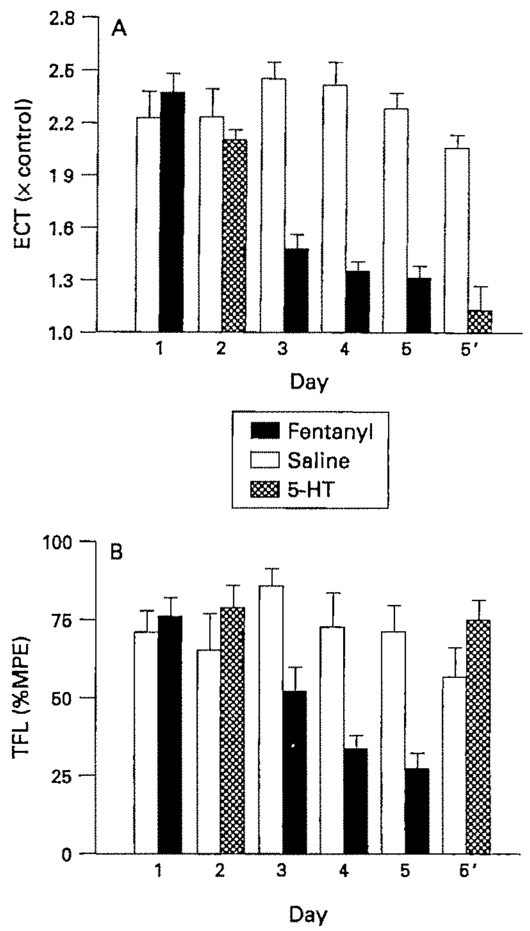

*Figure 6* Tolerance to intrathecal fentanyl. A: ECT responses in rats treated with intrathecal injections of fentanyl six times daily and saline. Responses on days 1, 3, 4 and 5 were measured at the beginning of the day to a single dose of fentanyl 0.74 nmol. The cross-hatched bars denote responses on days 2 and 5 (end of day 5 (5′)) to intrathecal 5-HT 1.89 μmol. B: The same procedure with fentanyl and 5-HT but results shown are for the TFL test. Results are mean, SEM ($n$=5 for saline treatment and $n$=10 for drug treatment).

intrathecal 5-HT on days 3, 4 and 5 in the ECT test. There was no significant change in responses to intrathecal 5-HT assessed by both tests in animals treated with repeated doses of saline throughout the study.

Similar experiments (fig. 6A, 6B) were performed using fentanyl 0.74 nmol as the agonist (group 2) compared with saline controls (group 4). After the first day's treatment of seven doses of intrathecal fentanyl at hourly intervals, responses to intrathecal fentanyl were reduced significantly compared with control responses in both tests ($P$<0.0001 in the ECT test and $P$=0.0068 in the TFL test; paired $t$ test). There was no significant change in the response in either test to intrathecal fentanyl in animals treated with seven intrathecal injections of saline at hourly intervals each day.

Animals who had become tolerant to intrathecal fentanyl by treatment with repeated intrathecal injections of fentanyl also showed a significant reduction in response to intrathecal injections of 5-HT, but only in the ECT test (fig. 6A). The response to intrathecal 5-HT 1.89 μmol was reduced from a mean control value of 2.08 (SEM 0.08) (ECT×control measured on day 1) to 1.1 (0.15) (ECT×control on day 5). In other words, no significant antinociception was produced on day 5. The effect of intrathecal injection of 5-HT on TFL was not changed significantly by fentanyl treatment ($P$=0.6022; paired $t$ test) (fig. 6B).

Animals rendered tolerant to intrathecal 5-HT as a result of repeated intrathecal injections of 5-HT 1.89 μmol exhibited a highly significant reduction in the response to fentanyl in the ECT test ($P$<0.0001; paired $t$ test) (see fig. 5A). In contrast, the response to fentanyl assessed by the TFL test was not significantly affected by repeated 5-HT treatment ($P$=0.358) (fig. 5B).

## Discussion

It is essential to demonstrate that a spinally administered drug is confined to the spinal cord in order to interpret results from whole animals in terms of action and interactions occurring at the spinal cord level. In the experiments described in this article, we have shown that the effects of drugs on ECT were differential or segmental. There were no disturbances in behaviour or locomotion in the presence of an increase in the current threshold for nociception in the tail without any change in the neck threshold. Therefore, we conclude that drug actions in all experiments where such differential effects occurred were confined to the caudal segments of the spinal cord where the drug was administered. As measurements of TFL were made at the same time, we may conclude that changes in TFL in these experiments were also the result of a spinal cord action of the drug, rather than the result of the drug spreading to the brain. Previous studies have shown that both TFL and ECT effects are caused by binding of 5-HT to spinal cord 5-HT receptors.[3 7 10]

Different stimuli (heat and electrical current) most likely activate different afferent pathways, and this study has revealed differences in the effects of intrathecal 5-HT on ECT and TFL. Different receptors seem to be involved at the level of the spinal cord. The classical way to analyse drug–receptor interactions is to construct a family of dose–response curves for a particular agonist at different known antagonist concentrations.[27] However, several of the conditions necessary for a valid analysis of this type could not be met in this situation. In particular, only drug doses, not concentrations, were known and the system was not at steady state. An alternative approach to analyse drug interactions with receptors and native neurotransmitter systems is to analyse antagonist dose–response curves,[28 29] that is to give a standard dose of drug and measure the effect in the presence of a range of doses of antagonist. In such an analysis, the position of an antagonist dose–response curve (the $ED_{50}$ for suppression of the effects of an agonist) is the same for suppression of the effects of an agonist drug that binds directly to a receptor as that for suppression of the effects of a drug that produces its effects by causing the release of a native neurotransmitter which binds with the same subtype of receptor to cause the final effect. Thus although naloxone is not a highly selective antagonist for the $\mu$ subtype of opioid receptor, it has been possible to demonstrate significant differences between naloxone dose–response curves for suppression of antinociceptive effects in the spine mediated by $\kappa$ opioid receptors compared with those mediated by $\mu$ receptors.[22]

In this study we demonstrated that naloxone caused dose-related suppression of the segmental antinociceptive effects of fentanyl assessed by both ECT and TFL tests and that these naloxone dose–response curves were coincident. This implies that both types of antinociception are mediated by fentanyl interacting with $\mu$ opioid receptors in the spinal cord. The naloxone dose–response curves for suppression of the effects of fentanyl on ECT and TFL were similar to those published previously ($ED_{50}$ approximately 0.2 $\mu$mol $kg^{-1}$); significantly different and to the left of naloxone dose–response curves for suppression of $\kappa$ opioid-mediated spinal antinociception.[22]

Naloxone also caused dose-related suppression of the increase in ECT produced by 5-HT but had no effect on 5-HT-induced TFL increases measured in the same experiments. This naloxone dose–response curve (5-HT, ECT effect) was coincident with both curves (ECT and TFL) for fentanyl, that is they overlay each other with approximately the same $ED_{50}$. The experiments with $\beta$-FNA confirmed the results of the naloxone experiments but were more convincing because of the greater selectivity of this antagonist for the $\mu$ opioid receptor.[24] The $\beta$-FNA dose–response curves for suppression of the effects of fentanyl on ECT and TFL and the effect of 5-HT on ECT were coincident and lay significantly to the left of the curve for suppression of the ECT effect of the $\kappa$ opioid U-50488H. In common with naloxone, $\beta$-FNA did not significantly attenuate the effects of 5-HT on TFL. Selectivity of $\beta$-FNA for the $\mu$ receptor was confirmed in these experiments because the dose of $\beta$-FNA which caused 50% suppression of the antinociceptive effects of fentanyl in both tests and the antinociceptive effects of 5-HT in the ECT test was approximately $10^{-15}$ mol whereas the dose needed to produce a similar amount of suppression of $\kappa$ opioid-mediated spinal antinociception was approximately $10^{-11}$ mol.

The results of the experiments using naloxone and $\beta$-FNA suggest that some of the antinociceptive effects of 5-HT in the spinal cord are mediated by activation of spinal cord opioid pathways involving $\mu$ opioid receptors. This only applies to the effects of 5-HT on ECT as the effects on TFL were not suppressed by naloxone or $\beta$-FNA. Naloxone is not highly selective for the $\mu$ receptor but $\beta$-FNA is a non-competitive antagonist, although it is highly selective for the $\mu$ opioid receptor. It is uncertain, therefore, if the antagonist dose–response curve analysis is valid with this drug even though the results confirm those obtained with naloxone. The tolerance experiments were therefore necessary.

The results from the tolerance studies are in agreement with those from the studies using antagonists. Cross tolerance for the effects of each agonist on ECT was produced. Thus induction of tolerance by repeated intrathecal injection of 5-HT led to a reduction in the increase in ECT caused by intrathecal fentanyl (fig. 5). The same was true of the animals treated with repeated intrathecal injections of fentanyl that led to progressive reduction in the antinociceptive effect of fentanyl assessed by both nociceptive tests. In these animals, induction of tolerance to fentanyl led to a decrease in the effect of 5-HT on ECT (fig. 6). No such cross tolerance occurred with the TFL test; 5-HT still caused an increase in TFL in fentanyl tolerant rats. These results suggest that desensitization of spinal cord $\mu$ opioid receptors may be caused either by repeated exposure to exogenous $\mu$ opioid agonist or by repeated release of an endogenous opioid agonist by exogenously applied 5-HT. This common $\mu$ opioid receptor is involved only with the antinociceptive effects of 5-HT and fentanyl measured in the ECT test and not those measured in the TFL test.

Therefore, these experiments support earlier observations of naloxone reversibility of 5-HT-mediated antinociception.[12 13] This may have implications for the development of clinical analgesic drugs acting at 5-HT receptors. Our results suggest that 5-HT-based analgesics could potentiate the antinociceptive action of spinal $\mu$-selective opioids. However, the full antinociceptive effect of such drugs may not be realized in opioid-tolerant individuals.

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# Haemodynamic conditions enhancing gas embolism after venous injury during laparoscopy: a study in pigs†

J. E. BAZIN, T. GILLART, P. RASSON, N. CONIO, L. AIGOUY AND P. SCHOEFFLER

**Summary**

This study was designed to determine the conditions that promote carbon dioxide embolism after venous injury during laparoscopy in pigs. Injury to an iliac vein was filmed during laparoscopy in the presence of a pneumoperitoneum created at increasing pressures from 0 to 30 mm Hg in 5-mm Hg increments. At intraperitoneal pressures less than 20 mm Hg, there was a parallel increase in femoral venous pressures, resulting in haemorrhage, with persistent blood flow to the inferior vena cava. At intraperitoneal pressures of 20–30 mm Hg, there was collapse of the femoral vein, occurring earlier in the presence of hypovolaemia. Between these two states (haemorrhage and collapse), there was a point of equilibrium which allowed retrograde venous penetration of carbon dioxide bubbles. During release of the pneumoperitoneum, these bubbles were exteriorized through the area of the injury, but some passed into the inferior vena cava where their presence was detected by an oesophageal Doppler probe. (*Br. J. Anaesth.* 1997; **78**: 570–575).

**Key words**

Surgery, laparoscopy. Carbon dioxide, pneumoperitoneum. Complications, gas embolism. Measurement techniques, Doppler. Pig.

Laparoscopy is a routine method for diagnosis and treatment of gynaecological and intra-abdominal disease. Unfortunately, it may be associated with several complications, in particular gas embolism caused by carbon dioxide embolism. Several cases of carbon dioxide embolism have been reported,[1–3] with an incidence varying from 0.0013 to 0.59%.[4 5]

There are several studies on the physiological effects of experimental venous air embolism in the anaesthetized sheep[6 7] and on prevention of accidental venous air embolism in humans, notably in neurosurgery.[8] However, there are few data on the pathophysiology of spontaneous gas embolism via venous injury during laparoscopic pneumoperitoneum. Also, it is not known if the preventive measures recommended for neurosurgical procedures, such as increasing central venous pressure by fluid loading or by PEEP, are effective in preventing gas entry during laparoscopy.

The aim of this study was to investigate the pressure (both haemodynamic and intra-abdominal) at which venous gas penetration through a surgically opened iliac vein occurs during laparoscopy.

## Materials and methods

After obtaining institutional approval, we studied six domestic pigs, weighing 15–30 kg; they were premedicated with ketamine 6 mg $kg^{-1}$ i.m. and anaesthetized with propofol 3 mg $kg^{-1}$ i.v. The trachea was intubated and anaesthesia maintained with 0.75–1.5% isoflurane and 50% nitrous oxide in oxygen. Ventilation was controlled via a circle system (Cicero-Dräger) and adjusted to maintain end-tidal carbon dioxide pressure ($P\text{E}'_{CO_2}$) at 4.0–4.4 kPa. Neuromuscular block was maintained by intermittent doses of vecuronium. Core temperature was monitored continuously by rectal probe and maintained greater than 36 °C by a heated mattress. ECG and $P\text{E}'_{CO_2}$ were monitored continuously (Dräger PM 8010) throughout the study. The carotid artery, right internal jugular vein and femoral vein were cannulated with fluid-filled 1.7-mm catheters and connected to three pressure transducers (Abbott L978-39) to measure continuous arterial pressure (AP), femoral venous pressure (FVP) and central venous pressure (CVP). Only 4 cm of the femoral catheter was introduced, so that the tip would remain extra-abdominal at the level of the femoral vein. This was checked by dissection in each pig at the end of the study. For detection of venous gas embolism, a transoesophageal Doppler ultrasound flow probe (ODM II, Abbott-France Laboratories) was introduced. Its length corresponded to the distance measured between the dental arches and the xiphoid proces +5 cm. The probe was positioned facing the inferior vena cava. Correct positioning was checked by respiratory variations in signal intensity and quality of flow through the vena cava, and confirmed by femoral injection of

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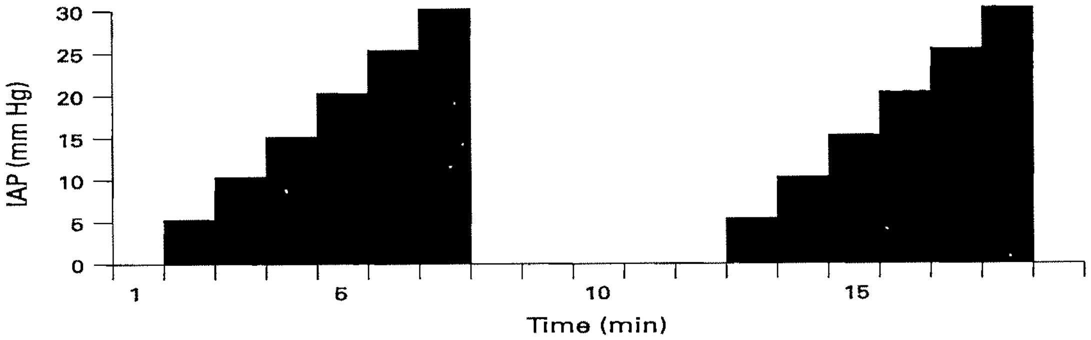

*Figure 1* Insufflation diagram: each pig underwent two cycles of pneumoperitoneum insufflation (IAP=intra-abdominal pressure) at pressures of 0 to 30 mm Hg, in increments of 5 mm Hg, each lasting 1 min. A 5-min interval separated the two cycles, which were followed by complete exsufflation.

2 ml of saline which was designed to induce a characteristic change in the signal recorded, after transient acceleration of venous flow.

During the first phase of the study, a carbon dioxide pneumoperitoneum was insufflated via a Verres' needle, at increasing pressures of 0–30 mm Hg in 5-mm Hg increments, using an automatic pressure flow insufflator (Stortz 26 430 BP). Mean AP, FVP, CVP and heart rate for each level of intra-abdominal pressure were noted after stabilization, and the pneumoperitoneum was then removed.

The second part of the study was undertaken after a stabilization period of 20 min. The pigs were placed in a moderate head-down position (10°) and the pressure transducers were repositioned so that they were level with the heart and femoral vein. A laparoscope (Stortz) was introduced via a 10-mm trocar inserted through a 1-cm supra-umbilical incision. As soon as the laparoscope was in place, it was connected to a camera, and the whole procedure was recorded on video–audio tape. Two additional trocars were inserted, under direct visual control, one in the lower left side of the abdomen for introduction of dissecting forceps, and the other into the right side for insertion of scissors. After dissection, the common iliac vein on the side opposite the femoral catheter was exposed and a vascular injury of a length of 3–4 mm (approximately half the diameter of the vein) was created. In three pigs (Nos 1, 3 and 5) blood loss was replaced by infusion of 500 ml of hydroxyethylstarch over 20 min. In the other three pigs (Nos 2, 4 and 6) blood loss was not replaced. Pneumoperitoneum was created with increasing pressures from 0 to 30 mm Hg in 5-mm Hg increments, each level of intra-abdominal pressure lasting at least 1 min. Each pig underwent two cycles of intraperitoneal insufflation separated by a 5-min interval. After each cycle, the peritoneum was completely emptied (fig. 1).

The presence of audible changes in the frequency of the Doppler signal was noted as evidence of gas embolism in the vena cava, and the point at which the changes occurred during each insufflation and exsufflation cycle was noted.

At the end of the procedure, correct positioning of the Doppler probe was confirmed by recording the characteristic signal displayed during injection of 1 cm$^3$ of carbon dioxide via the femoral venous catheter.

The effects of FVP, AP and CVP as a function of the insufflation pressures of the pneumoperitoneum were analysed by the Pearson linear regression test.

## Results

Five of the six pigs underwent two insufflation and exsufflation cycles at intraperitoneal pressures of up to 30 mm Hg. One pig died before the second cycle was completed (ventricular fibrillation, No. 4).

During the first phase of the study, during which intraperitoneal pressure was increased by 5-mm Hg increments, there was a parallel increase in FVP measured at the end of each level of intraperitoneal pressure. In all animals, FVP was always at least 4 mm Hg higher than intraperitoneal pressure. However, in pig No. 3, blood flow through the inferior vena cava, as detected by the Doppler probe, stopped at an intraperitoneal pressure of 30 mm Hg, while FVP did not exceed 31 mm Hg. In the six pigs, CVP increased very little and was not proportional to the increase in intraperitoneal pressure. Arterial

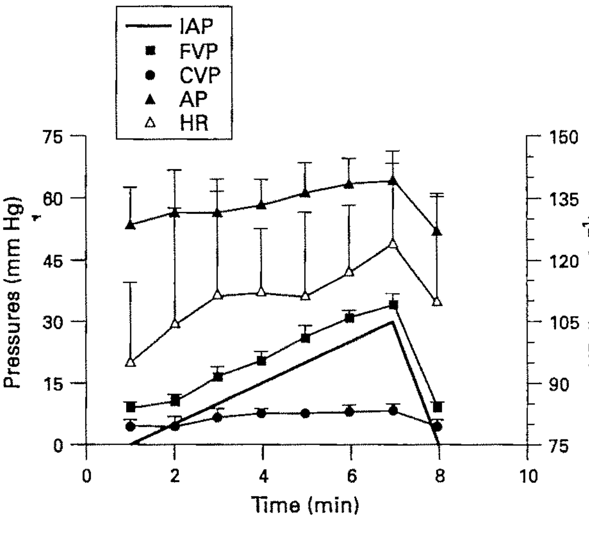

*Figure 2* Changes in mean femoral venous (FVP), central venous (CVP) and arterial (AP) pressures, and heart rate (HR) with pneumoperitoneum insufflation pressure (IAP=intra-abdominal pressure) in six pigs before iliac vein injury (mean, SD).

*Table 1* Effects of pneumoperitoneum pressure (IAP=intra-abdominal pressure) on femoral (FVP) and central venous (CVP) pressures after experimental injury to the iliac vein. Subsequent events included venous collapse (c), vascular penetration of bubbles (*), haemorrhage accompanied by exteriorization of bubbles (**), and Doppler recording of emboli moving up the vena cava (†)

| | | IAP (mm Hg) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 5 | 10 | 15 | 20 | 25 | 30 | 0 |
| First cycle | | | | | | | | | |
| No. 1 | FVP | 8 | 9 | 17 | 21 | 25 | 30 | 37 | 7 |
| | CVP | 5 | 5 | 6 | 6 | 7 | 8 | 9 | 5 |
| | Events | | | | | | | | **† |
| No. 3 | FVP | 8 | 8 | 11 | 17 | 22 | 26 | 32 | 8 |
| | CVP | 2 | 3 | 6 | 7 | 6 | 7 | 7 | 5 |
| | Events | | | | | | * | c | ** |
| No. 5 | FVP | 12 | 14 | 18 | 22 | 27 | 33 | 37 | 12 |
| | CVP | 6 | 7 | 8 | 10 | 10 | 11 | 11 | 5 |
| | Events | | | | | | | | |
| No. 2 | FVP | 11 | 15 | 20 | 24 | 29 | 31 | 32 | 10 |
| | CVP | 5 | 5 | 6 | 6 | 7 | 7 | 8 | 3 |
| | Events | | | | | | | c | **† |
| No. 4 | FVP | 8 | 10 | 15 | 21 | 25 | 32 | 35 | 7 |
| | CVP | 5 | 5 | 6 | 6 | 7 | 7 | 8 | 3 |
| | Events | | | | | | | | ** |
| No. 6 | FVP | 7 | 9 | 16 | 20 | 24 | 27 | 31 | 7 |
| | CVP | 1 | 2 | 3 | 3 | 3 | 4 | 4 | 1 |
| | Events | | | | | | * | c | **† |
| Second cycle | | | | | | | | | |
| No. 1 | FVP | 8 | 9 | 17 | 22 | 25 | 30 | 33 | 7 |
| | CVP | 4 | 5 | 6 | 6 | 7 | 7 | 7 | 4 |
| | Events | | | | | | * | c | **† |
| No. 3 | FVP | 8 | 9 | 11 | 16 | 22 | 26 | 32 | 8 |
| | CVP | 2 | 3 | 5 | 6 | 7 | 7 | 8 | 2 |
| | Events | | | | | | | c | **† |
| No. 5 | FVP | 12 | 13 | 16 | 21 | 26 | 32 | 37 | 12 |
| | CVP 6 | 7 | 8 | 10 | 10 | 10 | 11 | 4 | |
| | Events | | | | | | | | |
| No. 2 | FVP | 8 | 10 | 16 | 19 | 25 | 28 | 29 | 10 |
| | CVP | 1 | 1 | 2 | 2 | 2 | 3 | 3 | 2 |
| | Events | | | | | *† | c | c | **† |
| No 4 | FVP | 7 | 9 | 15 | 18 | 23 | 27 | Death | |
| | CVP | 2 | 2 | 3 | 4 | 5 | 5 | | |
| | Events | | | | | | * | | |
| No. 6 | FVP | 7 | 10 | 16 | 19 | 24 | 27 | 28 | 7 |
| | CVP | −1 | −1 | 0 | 0 | 1 | 1 | 1 | −2 |
| | Events | | | | | | c | c | **† |

pressure and heart rate increased. The increase in FVP and AP correlated significantly with the increase in pneumoperitoneal insufflation pressures ($r=0.97$, $P<0.001$ and $r=0.85$, $P<0.05$, respectively). After exsufflation, AP returned to approximately its initial values, but tachycardia persisted (fig. 2). In pig No. 3, a decrease of 11% in AP was accompanied by cessation of blood flow through the inferior vena cava.

In the second part of this study (table 1), the venous injury was the cause of venous bleeding which persisted at intraperitoneal pressures less than 20 mm Hg (fig. 3A). Higher intraperitoneal pressures caused clearly visible venous collapse and bleeding. Venous air aspiration ceased as flow through the inferior vena cava stopped (fig. 3C). During the first cycle, this process was seen at 30 mm Hg in pig Nos 3, 2 and 6. During the second cycle, complete collapse was seen at 25 mm Hg in pig Nos 2 and 6, and at 30 mm Hg in pig Nos 1 and 3. Between these two levels of pressure, an equilibrium condition, characterized by the beginning of a collapse during expiration, was observed. During that period, bubbles of gas were clearly seen being aspirated intravascularly, in a retrograde manner towards the lower limbs (fig. 3B). During release of the pneumoperitoneum, these bubbles were seen to reappear and most were exteriorized with the haemorrhage (fig. 3D). However, some gas bubbles followed venous flow, causing the characteristic change in the Doppler signal. Four of the six pigs developed bubbles which were detected by Doppler during the procedure and were recorded during the 3 s, after exsufflation at the end of the cycle. In pig No. 2, gas embolization was also detected during the state of equilibrium.

There were no changes in $PE'_{CO_2}$ throughout the procedure, even when gas embolism occurred. These findings prompted us to carry out a third insufflation in pig Nos 3 and 5, at the pressure corresponding to the state of equilibrium between collapse and bleeding, for a duration of 5 min: in both pigs gas aspiration was clearly visible, and the characteristic change in the Doppler signal was recorded. Pig No. 3 displayed a decrease in $PE'_{CO_2}$ from 4.2 to 3.5 kPa accompanied by a 25% decrease in AP.

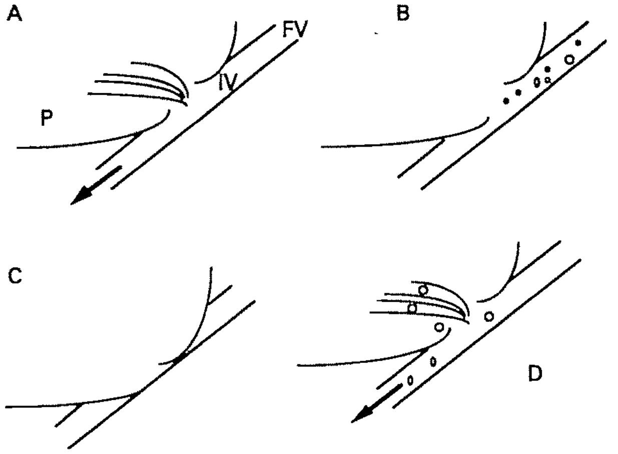

*Figure 3* Behaviour of a deperitonized iliac vein injury after insufflation of a pneumoperitoneum at increasing pressures, followed by exsufflation (IV=iliac venous, FV=femoral venous, P=pneumoperitoneum, o=carbon dioxide embolism). A: Persistent haemorrhage after iliac vein incision at intra-abdominal pressures less than 20 mm Hg; B: equilibrium state at intermediate intraperitoneal pressures, characterized by venous collapse during expiration and retrograde intravascular penetration of gas bubbles in four pigs; C: venous collapse and cessation of bleeding at high intra-abdominal pressures; D: exteriorization of carbon dioxide bubbles accompanied by bleeding during release of the pneumoperitoneum and detection of emboli in the inferior vena cava.

## Discussion

We chose to expose the iliac vein after peritoneal dissection, because of its size and accessibility. Furthermore, the technique is easily reproducible. However, caution should be exercised in any extrapolation of these results to humans, because the iliac vein is normally less sensitive to variations in intraperitoneal pressure than the vessels normally exposed during laparoscopy. We did not measure transmural pressures in the right atrium, because direct measurement of intravascular pressures constitutes the only true measure of blood flow and its direction.

In this study, FVP increased with increasing intraperitoneal pressure, thus maintaining blood flow through the inferior vena cava, up to levels of 25 mm Hg. Intraperitoneal pressures greater than 25 mm Hg resulted in venous collapse, which occurred at lower levels of intraperitoneal pressure in the presence of hypovolaemia. Our findings are in agreement with previous studies on the haemodynamic effects of pneumoperitoneum with or without hypovolaemia. Rubinson and co-workers described parallel increases in intraperitoneal and abdominal vena cava pressures after intraperitoneal perfusion of liquid. At pressures of 29–42 mm Hg, they demonstrated collapse of the transdiaphragmatic vena.[9] Jorgensen and colleagues reported in pigs a decrease in femoral venous blood flow concomitant with an increase in intraperitoneal pressure from 5 to 20 mm Hg, but with no cessation of blood flow at the highest level of pressure.[10] In dogs, Ivankovich and co-workers found that insufflation of a pneumoperitoneum at 40 mm Hg reduced cardiac and vena caval blood flow by 60%, but FVP remained consistently greater than intraperitoneal pressure.[11] In two groups of pigs, with and without hypovolaemia, Ho and colleagues found that the hypovolaemic group were more acidotic and hypercapnic after pneumoperitoneum, with a persistent but smaller increase in AP and unchanged cardiac index.[12] In dogs, with vena caval pressure kept constant by cardiopulmonary bypass, Takata, Wise and Robotham investigated the effects of a moderate increase in intra-abdominal pressure. During hypervolaemia, there was an increase in vena caval blood flow caused by splanchnic redistribution of blood from the liver. In hypovolaemic animals, the decrease in transmural pressure of the transdiaphragmatic vena cava resulted in partial collapse of the latter with a decrease in venous return. However, FVP increased in parallel with the pressure in the vena cava.[13] These results confirm that the variations in intraperitoneal pressure and FVP are the main determinants of vascular wall movements responsible for venous collapse and bleeding, and that between these two extremes there is a situation which may facilitate gas embolization. The filling pressures of the right heart, which provides an approximate measure of volaemic status, thus plays an indirect role in determining the threshold for venous collapse. The intrinsical tone of the venous wall seems to play no role in these changes. With respect to the lower vena cava, the parietal component involved in venous collapse has been assessed at only 1 mm Hg.[13]

The incidence of gas embolism during laparoscopic surgery varies widely. No embolism was detected by precordial Doppler monitoring during 61 laparoscopic cholecystectomy procedures.[14] However, Thio and Reichert reported systematic appearance of emboli in seven patients monitored by transoesophageal echocardiography.[15] With the same monitoring system, Derouin and colleagues also detected 11 cases of gas embolism in 16 patients.[16] Various multicentre investigations of incidents during laparoscopic surgery show that gas embolism is a prime suspect in most "cardiovascular" collapse occurring during laparoscopy.[17]

Most of the serious cases of gas embolism reported in the literature occur at the beginning of an operation, because of intravascular insufflation caused by incorrect positioning of the insufflation needle. The cases reported to have occurred in the middle or at the end of surgery involve other mechanisms. According to some authors, embolism can occur after peritoneal absorption of gas with accumulation in the portal system and secondary mobilization during changes in position or after abdominal decompression.[18] However, this suggestion has not been confirmed and seems less probable than embolization of gas from the peritoneal cavity after venous damage during surgical dissection. Some of these delayed embolic episodes may represent gas bubbles which have been aspirated in a retrograde manner at the time of perioperative venous injury. Our findings support this mechanism, especially in cases when the conditions created by serious injury to a major vessel occur at intraperitoneal pressures greater than 15 mm Hg.

Transoesophageal Doppler can detect air emboli as small as 0.05 ml[19] with no haemodynamic changes or change in $P\mathrm{E}'_{\mathrm{CO}_2}$, which usually detects an embolus volume of 1 ml kg$^{-1}$.[20 21] However, in the presence of rapid variations in intraperitoneal pressure and if favourable haemodynamic conditions persist, we may expect larger degrees of air emboli. This occurred in one of the two pigs in which we maintained a pneumoperitoneum at the equilibrium pressure for 5 min. The possibility of a Venturi effect suggested by some authors[22] at low intraperitoneal pressures was not confirmed by our study.

Most of the prophylactic measures to combat venous gas embolism have been developed during neurosurgery performed with the patient in the sitting position, and thus are aimed at avoiding aspiration of air through the dura mater venous sinuses. All methods involve increasing the pressure in the venous sinuses above atmospheric pressure, such as vascular filling, introduction of PEEP or the use of antishock trousers. However, these methods are controversial, for example PEEP may also increase the risk of paradoxical gas embolism, as right atrial pressure may become higher than the left, thus allowing a shunt to develop in the presence of a patent foramen ovale, which is present in 10–30% of patients in the general population.[23–26] This risk is accentuated by the fact that gas embolism increases CVP when it reaches the pulmonary circulation. Volumes of approximately 2 ml kg$^{-1}$ may reverse the pressure between the left and right cavities.[27 28] During laparoscopy, all of these prophylactic methods are of no avail. We have shown that the risk of air embolism remained low if intraperitoneal pressure was less than 15 mm Hg.

In cases where severe vascular injury causes serious haemorrhage, it is risky to increase intraperitoneal pressure in order to stop gas aspiration or haemorrhage and thus allow time for laparoscopic repair of the injury. The intraperitoneal pressure required may be so high that it may have harmful cardiovascular effects, especially a decrease in cardiac output because of reduction in venous return. In addition, we cannot be sure that such conditions would not favour massive gas aspiration. However, if such an increase in intraperitoneal pressure is warranted, close monitoring of haemodynamic state and continuous cardiac auscultation with a transoesophageal Doppler probe is necessary in order to detect possible gas embolism, until the pneumoperitoneum is evacuated.

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# Increased intraperitoneal pressure up to 15 mm Hg does not reliably induce haemodynamic changes in pigs

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## Summary

Haemodynamic alterations occur consistently with laparoscopic surgery in humans. These haemodynamic changes have never been reproduced in an animal model without additional potentiating factors. As these alterations may be deleterious in some patients and as the cause is only partly understood, we have used an animal model to study these changes. Pneumoperitoneum with intraperitoneal pressures of up to 15 mm Hg were produced in pigs, in the same way as for laparoscopic surgery in humans. Arterial pressure, cardiac output, pulmonary arterial pressure and systemic arterial resistance were assessed at baseline and after pneumoperitoneum had been produced. Intraperitoneal pressures of up to 15 mm Hg were not associated with consistent circulatory changes and we conclude that haemodynamic changes associated with laparoscopic surgery are dependent on species. (*Br. J. Anaesth.* 1997; **78**: 576–578).

**Key words**
Carbon dioxide, pneumoperitoneum. Surgery, laparoscopy. Cardiovascular system, effects. Pig. Model, pig.

Haemodynamic changes occur consistently in humans during laparoscopic surgery, even though intraperitoneal pressure (IPP) is maintained at less than 15 mm Hg.[1] It is unlikely that these haemodynamic changes are entirely related to decreased venous return, direct compression of the abdominal aorta secondary to increased IPP[2] or transperitoneal absorption of carbon dioxide. It has been suggested that baroreflexes elicited by intra-abdominal viscera stimulation are involved.[3] In an attempt to evaluate this latter hypothesis, we created pneumoperitoneum in pigs in the same way as for laparoscopic surgery in humans.[1] The pig haemodynamic system has been shown to resemble the human system.[4]

## Materials and methods

After obtaining approval from the Institutional Animal Care Committee, two adult domestic pigs (mean weight 40 (SD 0.5) kg) and six piglets (18.1 (1.9) kg) were anaesthetized with ketamine i.m. and continuous infusion of fentanyl and pancuronium, and their lungs ventilated mechanically (Cicero mechanical ventilator, Dräger SA, France) with 50% nitrous oxide in oxygen after tracheal intubation. Tidal volume was set at 10 ml $kg^{-1}$. Ventilatory frequency was adjusted to maintain end-tidal carbon dioxide partial pressure ($PE'_{CO_2}$) at 4.5±0.3 kPa. Lactated Ringer's solution was infused at 500 ml $h^{-1}$. The carotid artery was cannulated for monitoring systemic arterial pressure (AP) and for blood sampling. The right external jugular vein was cannulated with a 7-French pulmonary artery thermodilution catheter. Pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure (PCW) and cardiac output (CO) were measured (Marquette electronics, France). SVR (dyn $s^{-1}$ $cm^{-5}$) was calculated using the standard formula. Peritoneal insufflation with carbon dioxide was performed slowly up to 15 mm Hg, at a rate of 250 ml $min^{-1}$, via a Palmer needle placed percutaneously into the abdominal cavity with an insufflator allowing continuous monitoring of IPP (Laparoflator FM, Wiest KG, Germany). Haemodynamic measurements were obtained after a 15-min period of stabilization: at baseline after induction of anaesthesia and at an insufflation level of 15 mm Hg. Body temperature was maintained at 36 °C.

Mean values were analysed using a paired Student's *t* test. Significance was set at $P<0.05$.

## Results

Intraperitoneal insufflation was not associated with any significant changes in either AP ($P=0.59$), CO ($P=0.62$) or SVR ($P=0.63$) (table 1).

## Discussion

PAP and PCW increased as a consequence of increased intrathoracic pressure associated with establishment of pneumoperitoneum.[1] However, our study failed to reproduce those changes usually observed in humans (i.e. increase in AP and SVR;

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*Table 1* Haemodynamic effects of increased intra-abdominal pressure. AP 1=Systolic arterial pressure before IAP increase; AP 2=systolic arterial pressure for IAP increased to 15 mm Hg; SVR 1=systemic vascular resistance before IAP increase, SVR 2=systemic vascular resistance for IAP increased to 15 mm Hg; CO 1=cardiac output before IAP increase; CO 2=cardiac output for IAP increased to 15 mm Hg; PCW 1=pulmonary capillary wedge pressure before IAP increase; PCW 2=pulmonary capillary wedge pressure for IAP increased to 15 mm Hg; PA 1=pulmonary artery wedge pressure before IAP increase, PA 2=pulmonary artery wedge pressure for IAP increased to 15 mm Hg, $P\text{E}'_{CO_2}$=end-tidal $P\text{CO}_2$ for IAP increased to 15 mm Hg. *P*=(1) before IAP increase, *vs* (2) for IAP increased to 15 mm Hg

| | AP 1 (mm Hg) | AP 2 (mm Hg) | SVR 1 (dyn $s^{-1}$ $cm^{-5}$) | SVR 2 (dyn $s^{-1}$ $cm^{-5}$) | CO 1 (litre $min^{-1}$) | CO 2 (litre $min^{-1}$) | PA 1 (mm Hg) | PA 2 (mm Hg) | PCW 1 (mm Hg) | PCW 2 (mm Hg) | $P\text{E}'_{CO_2}$ (kPa) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Adult pig 1 | 92 | 97 | 1837 | 2012 | 3.7 | 3.3 | 18 | 21 | 12 | 18 | 4.8 |
| Adult pig 2 | 84 | 89 | 2608 | 2336 | 2.3 | 2.5 | 17 | 20 | 9 | 13 | 5.2 |
| Piglet 1 | 79 | 84 | 2933 | 2400 | 2.1 | 2.7 | 14 | 12 | 4 | 5 | 5.3 |
| Piglet 2 | 113 | 127 | 2971 | 1962 | 2.8 | 3.1 | 19 | 23 | 12 | 9 | 5.1 |
| Piglet 3 | 116 | 100 | 3418 | 3672 | 2.1 | 2.2 | 17 | 27 | 13 | 21 | 4.7 |
| Piglet 4 | 106 | 106 | 3266 | 2800 | 2.4 | 2.5 | 17 | 28 | 6 | 14 | 5.3 |
| Piglet 5 | 76 | 71 | 3341 | 3200 | 2.7 | 2.7 | 16 | 18 | 12 | 12 | 5.2 |
| Piglet 6 | 74 | 80 | 2061 | 2545 | 2.6 | 2.2 | 13 | 14 | 5 | 5 | 5.1 |
| Mean (SD) | 92 (17) | 97 (17) | 2804 (5910 | 2741 (532) | 2.6 (0.5) | 2.7 (0.3) | 16.4 (1.9) | 20.3 (5.7) | 9.1 (3.6) | 12.1 (5.7) | 5.1 (0.2) |
| *P* | 0.59 | | 0.63 | | 0.62 | | 0.03 | | 0.07 | | |

decrease in CO).[1] The pig model was chosen as this animal is related to humans, both physiologically and anatomically. Its cardiovascular system is similar with respect to the size and distribution of coronary vessels, arterial pressure, heart rate, cardiac index, regional distribution of carbon monoxide and maximum oxygen consumption.[4] However, examination of many studies conducted in animals to reproduce haemodynamic disturbances associated with increased IPP, shows discrepancies between studies for every level of IPP and even for baseline measurements. Moreover, haemodynamic changes similar to those in humans during laparoscopic surgery have never been reproduced in animals without additional potentiating factors: IPP increased to more than 20 mm Hg and in some studies up to 40 mm Hg[5]; hypovolaemia or a vasodilating agent, or both[6]; hypercapnia or acidosis[7]; and coexisting thoracic incision for haemodynamic investigation.[8] In published studies, IPP has been increased by various physical methods: carbon dioxide or nitrogen insufflation,[8] external counterpressure of the abdominal wall,[9] intraperitoneal fluid infusion[1] and intra-abdominal implantation of an inflatable bag.[10] Indeed, regional differences in abdominal pressure have been described when IPP is increased by methods other than intraperitoneal gas or liquid insufflation.[11] Moreover, a vascular reflex might have been elicited in some procedures by compression or distension of intraperitoneal viscera.[3] Only two animal species, dogs and pigs, have been assessed and in almost all studies, animals have been anaesthetized with either pentobarbitone or fentanyl, both of which are unlikely to upset haemodynamic changes observed in humans during laparoscopic procedures.[12]

It is questionable if the drugs given to our pigs may have affected the data. Ketamine stimulates the sympathetic system[13] causing increases in AP and SVR. As increases in AP and SVR were the main haemodynamic changes expected, and as no increases in AP or SVR occurred even in the presence of possible co-existing sympathetic stimulation induced by ketamine, we conclude that ketamine had no effect.[13] Fentanyl stimulates the parasympathetic system[14]; therefore fentanyl may have impaired the expected haemodynamic changes. However, continuous infusion of fentanyl has been shown to cause minimal haemodynamic changes[14] and is unlikely to have completely masked the anticipated findings. Pancuronium produces tachycardia via parasympathetic block. However, this effect is weak and is unlikely to have impaired the expected haemodynamic effects of increased IPP. We did not study IPP at values greater than 15 mm Hg, but several studies using higher IPP (up to 40 mm Hg) failed to reliably reproduce haemodynamic changes associated with pneumoperitoneum in humans.[5]

In our investigation, peritoneal insufflation and pressure control were assessed with an insufflator validated for this use. Haemodynamic assessment with a thermodilution pulmonary artery catheter is a routine and reliable technique in animal and human investigations. Body temperature and $P\text{CO}_2$ were maintained within the physiological range and fluid status was monitored closely. Our sample size may have been too small to draw definitive conclusions, but no consistent trend occurred in haemodynamic changes. In accordance with previous studies,[5 7] inclusion of two adult pigs in the study suggests that maturity is not a major factor.

In summary, we believe that our study, in accordance with previous similar studies, provides the following information: (a) haemodynamic changes associated with laparoscopic surgery in humans cannot reliably be reproduced in a pig model; (b) haemodynamic disturbances associated with IPP are dependent on species; (c) extrapolation to humans of data recorded in animal models during laparoscopic procedures must be made with caution.

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# *In vivo* assessment of droperidol-induced bronchial relaxation in dogs using a superfine fibreoptic bronchoscope

N. OTOMO, K. HIROTA, T. SATO, Y. HASHIMOTO AND H. ISHIHARA

## Summary

Droperidol has been reported to cause bronchodilatation but its mechanism(s) of action is unknown. We have evaluated the spasmolytic effect of droperidol on histamine- and serotonin (5-HT)-induced bronchoconstriction in dogs. Bronchial cross-sectional area was assessed with a superfine fibreoptic bronchoscope. Twenty-eight mongrel dogs were allocated randomly to one of two groups (histamine and 5-HT) to receive either histamine or 5-HT to induce bronchoconstriction. Changes in bronchial cross-sectional area were presented as percentage of basal bronchial cross-sectional area. Continuous i.v. infusion of histamine 500 $\mu$g kg$^{-1}$ h$^{-1}$ or 5-HT 500 $\mu$g kg$^{-1}$ h$^{-1}$ decreased percentage bronchial cross-sectional area by 46.4 (14.3) % or 68.9 (13.7) %, respectively. In both groups, droperidol reversed bronchoconstriction in a dose-dependent manner. In the histamine but not in the 5-HT group, plasma adrenaline and noradrenaline concentrations increased significantly after i.v. droperidol. In addition, propranolol antagonized droperidol-induced relaxation in the histamine but not in the 5-HT group. Our data indicate that the spasmolytic effect of droperidol on canine airway was caused, at least in part, by both catecholamine releases and 5-HT receptor antagonism. (*Br. J. Anaesth.* 1997; **78**: 579–582).

**Key words**
Lung, bronchus. Pharmacology, droperidol. Equipment, bronchoscopes Dog.

Droperidol is an effective agent for the treatment of status asthmaticus.[1] The bronchodilating effect of droperidol may be mediated via $\alpha_1$-adrenoceptor block,[1] catecholamine release[2 3] and serotonin (5-HT) receptor antagonism.[4–6] Gentil and colleagues demonstrated that droperidol prevented 5-HT- but not histamine-induced bronchospasm in guinea pigs.[4] In contrast, we have reported previously that droperidol inhibits tracheal contraction induced by both 5-HT and histamine.[6] Gentil and colleagues[4] evaluated bronchospasm by measuring respiratory conductance, a classical indirect measure with low sensitivity and reliability.[7 8] We have developed a direct method to quantify bronchial calibre using a superfine fibreoptic bronchoscope with increased sensitivity compared with measures of airway resistance, dynamic pulmonary compliance and airway pressure.[9 10] In this study, we have assessed *in vivo* the spasmolytic effects of droperidol on histamine- and 5-HT-induced bronchoconstriction in dogs by measuring airway calibre using a fibreoptic bronchoscope.

## Materials and methods

After approval of our Animal Experiment Committee, 28 mongrel dogs, weighing 8–12 kg, were anaesthetized with pentobarbitone 30 mg kg$^{-1}$ i.v. and paralysed with pancuronium 200 $\mu$g kg$^{-1}$ h$^{-1}$ i.v. The trachea was intubated using a tracheal tube (internal diameter 7.0 mm; Fuji system, Tokyo, Japan) with an additional small lumen for insertion of a superfine fibreoptic bronchoscope with an outer diameter of 2.2 mm (OES Angiofiberscope AF type 22A, Olympus, Tokyo, Japan) to monitor continuously bronchial cross-sectional area. The tip of the fibrescope was located between the second and third bifurcation of the right lung. Fibreoptic image of bronchial cross-sectional area was printed via a videoprinter (Videoprinter VY-170, Hitachi, Tokyo, Japan) and measured with an NIH image program which is well established and widely used (written by Wayne Rasband at the US National Institutes of Health and available from the Internet by anonymous ftp from zippy. nimh. nih. gov. or on floppy disk from NTIS, 5285 Port Royal Rd., Springfield, VA 22161, part number PB93-504868). Changes in bronchial cross-sectional area were represented as percentage of basal bronchial cross-sectional area (assessed before bronchoconstrictor infusion). The lungs were ventilated with an animal ventilator (AR-300, Acoma, Tokyo, Japan) and end-tidal carbon dioxide was maintained continuously at 4.5–5.0% before induction of bronchoconstriction. Systemic arterial pressure was monitored continuously via a femoral arterial cannula which was also used for blood sampling. A pulmonary artery catheter was inserted via the femoral vein to administer drugs and

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to infuse lactate Ringer's solution 4 ml $kg^{-1}$ $h^{-1}$. Dogs were allocated randomly to one of two groups; 14 dogs received histamine to induce bronchoconstriction (histamine group) and the remaining 14 dogs received 5-HT (5-HT group).

### HISTAMINE GROUPS

Bronchoconstriction was induced with a bolus dose of histamine 10 μg $kg^{-1}$ i.v. followed by an infusion of 500 μg $kg^{-1}$ $h^{-1}$ via the pulmonary artery catheter. Systolic arterial pressure was maintained greater than 80 mm Hg with infusion of fluid 50 ml $kg^{-1}$ and with continuous infusion of phenylephrine 0.5–2.0 μg $kg^{-1}$ $min^{-1}$ at a rate dependent on systolic arterial pressure and which could not significantly affect histamine-induced bronchoconstriction.[10] Thirty minutes later, when stable bronchoconstriction was achieved, droperidol was given i.v. Seven of the 14 dogs were given each dose of droperidol: 0 (saline), 0.01, 0.1 and 1.0 mg $kg^{-1}$ i.v. (histamine–droperidol group), and the remaining seven dogs were given droperidol 0 and 1.0 mg $kg^{-1}$ followed by 100 μg $kg^{-1}$ of propranolol (histamine–droperidol–propranolol group). In both groups, bronchial cross-sectional area was assessed before and 30 min after the start of histamine infusion and 5 min after administration of each dose of droperidol and propranolol. At least 15 min elapsed between administration of each dose. Arterial blood was obtained simultaneously with bronchial cross-sectional area assessments for measurement of plasma concentrations of adrenaline and noradrenaline in the histamine–droperidol group. Log-dose–response curves were constructed using DeltaGraph Pro. (DeltaPoint, Inc. 1992). Plasma adrenaline and noradrenaline concentrations were measured by gas chromatography–mass spectrometry.[11]

### 5-HT GROUPS

In the 5-HT groups, bronchoconstriction was induced with a bolus of 5-HT 10 μg $kg^{-1}$ i.v. followed by an infusion of 500 μg $kg^{-1}$ $h^{-1}$. Seven dogs were included in the 5-HT–droperidol group and the remaining seven dogs in the 5-HT–droperidol–propranolol group. The remainder of the study was as described for the histamine groups.

### ANALYSIS OF DATA

All data are expressed as mean (SD). Statistical analyses were by repeated-measures ANOVA followed by Fisher's protected least significant difference test for the histamine and 5-HT–droperidol groups, and by Scheffé's *F* test for the histamine and 5-HT–droperidol–propranolol groups. $P<0.05$ was considered significant.

## Results

### HISTAMINE GROUP

In the histamine–droperidol group, histamine decreased percentage bronchial cross-sectional area by 46.4 (14.3) % (fig. 1A). Droperidol produced a dose-dependent increase in percentage bronchial cross-sectional area (i.e. bronchodilatation) with an $ED_{50}$ of 0.157 (0.108) mg $kg^{-1}$; 1.0 mg $kg^{-1}$ produced full reversal of histamine-induced bronchoconstriction. Plasma adrenaline and noradrenaline concentrations also increased significantly in a dose-dependent manner (fig. 2). In the histamine–droperidol–propranolol group, histamine decreased percentage bronchial cross-sectional area by 35.7 (14.0) % which was reversed by droperidol (percentage bronchial cross-sectional area 98.4 (15.1) %). Propranolol 100 μg $kg^{-1}$ fully reversed the increase in bronchial cross-sectional area induced by droperidol (fig. 1B).

### 5-HT GROUP

5-HT decreased percentage bronchial cross-sectional area by 77.1 (13.0) % in the 5-HT–droperidol group and by 68.9 (13.7) % in the 5-HT–droperidol–propranolol group. Droperidol

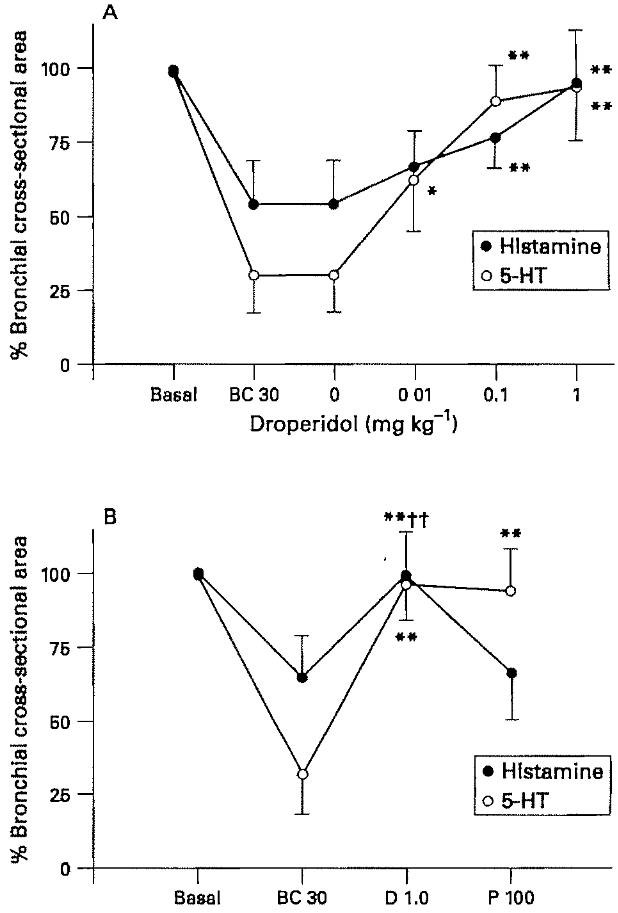

*Figure 1* Spasmolytic effect of droperidol on histamine- or serotonin (5-HT)-induced bronchoconstriction measured as percentage bronchial cross-sectional area. A: Droperidol produced dose-dependent reversal of bronchoconstriction induced by histamine or 5-HT. B: Propranolol 100 μg $kg^{-1}$ (P 100) reversed the spasmolytic effect of droperidol 1.0 mg $kg^{-1}$ (D 1.0) in the histamine but not in the 5-HT group. Data are mean, SD ($n=7$). Basal=before the start of histamine or serotonin (5-HT) infusion, BC30=30 min after the start of bronchoconstrictor (BC: histamine or 5-HT) infusion. *$P<0.05$, **$P<0.01$ compared with BC30; ††$P<0.01$ compared with P 100.

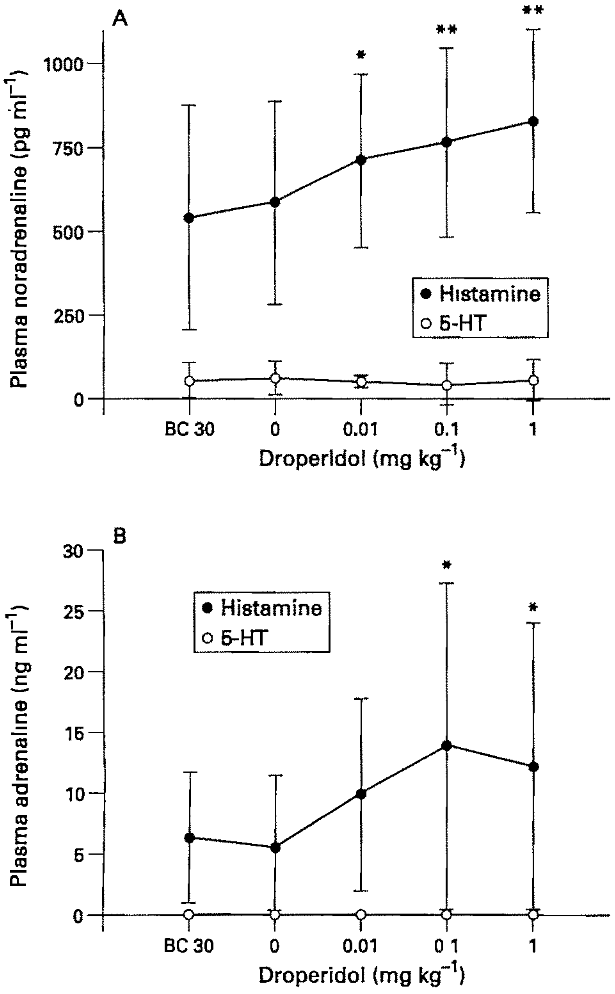

*Figure 2* Changes in plasma concentrations of noradrenaline (A) and adrenaline (B). BC30=30 min after the start of bronchoconstrictor (histamine or serotonin (5-HT)) infusion. Data are mean, SD ($n$=7). *$P$<0.05, **$P$<0.01 compared with BC30.

1.0 mg $kg^{-1}$ reversed 5-HT-induced decrease in bronchial cross-sectional area in both the 5-HT–droperidol (fig. 1A) and the 5-HT–droperidol–propranolol groups (fig. 1B). However, there were no significant changes in plasma adrenaline and noradrenaline concentrations, which were significantly lower than those in the histamine–droperidol group (fig. 2). Propranolol had no effect on droperidol-induced bronchodilatation (fig. 1B). The $ED_{50}$ for droperidol reversal of 5-HT-induced bronchoconstriction was 0.013 (0.011) mg $kg^{-1}$. Droperidol was significantly more potent at reversing 5-HT than histamine-induced constriction ($P$<0.01).

## Discussion

We have reported previously that droperidol inhibits histamine- and 5-HT-induced contraction of guinea pig tracheal smooth muscle *in vitro*.[6] Our study has confirmed that droperidol was capable of producing bronchodilatation in bronchospastic states induced by histamine or 5-HT *in vivo*. The mechanism of droperidol-induced relaxation may be via α-adrenoceptor block,[1] β-adrenergic stimulation by catecholamine release[2 3] and 5-HT receptor antagonism.[4–6] However, our previous *in vitro* study[6] indicated that prazosine (α-blocker) did not alter either 5-HT-induced tracheal contraction or the relaxant effect of droperidol. None the less, α-adrenoceptor block cannot be excluded as the α-adrenoceptor is involved in the mechanism of asthma.[12 13] Droperidol has been reported to induce catecholamine release.[2 3] In our study, the histamine groups indicated that droperidol produced a spasmolytic effect accompanied by catecholamine release and that propranolol completely antagonized droperidol-induced relaxation. Therefore, it is likely that catecholamine release is involved indirectly in droperidol-mediated relaxation. In contrast, in the 5-HT groups, droperidol-induced relaxation of 5-HT-induced bronchoconstriction was not caused by catecholamine release. Relaxation may be produced by a direct 5-HT receptor blocking action of droperidol. In agreement with our previous *in vitro* study,[6] in this study we found that the $ED_{50}$ of droperidol against 5-HT was one order of magnitude more potent than against histamine. These findings suggest that 5-HT-induced bronchoconstriction is more specifically antagonized by droperidol than histamine.

Gentil and colleagues found that droperidol prevented 5-HT- but not histamine-induced constriction but this was assessed indirectly using respiratory conductance.[4] However, Brown and colleagues[7 8] reported that indirect assessment of airway calibre by airway resistance and pulmonary compliance may be a less reliable assessment of bronchodilatation compared with direct vision using high resolution computed topography. We have also found that our direct vision method using a superfine fibreoptic bronchoscope was more sensitive than indirect measures.[10]

## Acknowledgement

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*British Journal of Anaesthesia* 1997; 78: 583–585

SHORT COMMUNICATIONS

# Measurement of bronchodilatation using a superfine fibreoptic bronchoscope

N. OTOMO, K. HIROTA, Y. HASHIMOTO, T. KUSHIKATA, T. SATO, H. ISHIHARA AND A. MATSUKI

## Summary

In this study, we report the development and accuracy of a direct technique to measure airway calibre using a superfine fibreoptic bronchoscope. Ten mongrel dogs were anaesthetized with pentobarbitone and the trachea intubated with a tracheal tube; the small lumen of the tube allowed passage of a superfine fibreoptic bronchoscope (od 2.2 mm). Bronchial cross-sectional area and airway pressure were recorded continuously and dynamic pulmonary compliance and airway resistance calculated. The dogs were allocated to one of two groups. In the first group (six dogs), bronchoconstriction was induced with histamine 10 $\mu$g kg$^{-1}$ i.v. and 500 $\mu$g kg$^{-1}$ h$^{-1}$ c.i.v. Thirty minutes later, adrenaline 0–0.4 mg kg$^{-1}$ was given i.v. Bronchial cross-sectional area, dynamic pulmonary compliance and airway resistance were assessed simultaneously. In the second group, 0.9% saline was given 30 min after placement of the superfine fibreoptic bronchoscope and 10 min later atropine 0.1 $\mu$g kg$^{-1}$ was administered. In the first group, histamine decreased mean percentage bronchial cross-sectional area by 49.2 (SD 11.5) %, reduced dynamic pulmonary compliance from 32.1 (12.6) to 22.3 (5.2) ml cm $H_2O^{-1}$ and increased airway resistance from 39.1 (11.6) to 57.2 (10.2) cm $H_2O$ litre$^{-1}$ s$^{-1}$. Adrenaline produced a dose-dependent increase in percentage bronchial cross-sectional area and dynamic pulmonary compliance to 119.4 (31.3) % and 27.4 (5.5) ml cm $H_2O^{-1}$, respectively, and a decrease in airway resistance to 43.9 (7.2) cm $H_2O$ litre$^{-1}$ s$^{-1}$. There were significant correlations between percentage bronchial cross-sectional area and dynamic pulmonary compliance ($r$=0.720, $P$<0.0001) and airway resistance ($r$=0.727, $P$<0.0001). Atropine 0.1 mg kg$^{-1}$ increased basal bronchial cross-sectional area to 137.5 (16.9) %. These data indicate that adrenaline reversed histamine- and pentobarbitone-induced bronchoconstriction. (*Br. J. Anaesth.* 1997; **78**: 583–585).

**Key words**
Lung, bronchus. Equipment, bronchoscopes. Airway, calibre.

Airway calibre is influenced by several factors, including smooth muscle tone, oedema of the airway wall and airway secretory activity.[1] Airway calibre is normally assessed indirectly by measuring airway resistance or compliance, and these can be influenced strongly by airway secretions.[2] Moreover, several articles have noted the relative insensitivity of indirect measurements of airway calibre.[3–5] Brown and colleagues developed a technique for direct measurement of airway calibre using high-resolution computed tomography and showed that changes in airway calibre were not always accompanied by changes in total pulmonary resistance.[4] While their direct method appeared more specific than conventional indirect measures of airway calibre, the system is too large to use conveniently as an airway monitor in the operating theatre or in the intensive care unit. In this study, we report the development of a new portable direct method to quantify bronchial calibre using a superfine fibreoptic bronchoscope.

## Methods and results

After obtaining approval from our Animal Care Committee, 10 mongrel dogs (8–12 kg) were anaesthetized with pentobarbitone 30 mg kg$^{-1}$ i.v. and paralysed with pancuronium 200 $\mu$g kg$^{-1}$ h$^{-1}$ d.i.v. The trachea was intubated with a special tracheal tube (internal diameter 7.0 mm; Fuji system, Tokyo) with a small lumen into which a superfine fibreoptic bronchoscope (outer diameter 2.2 mm; OES Angiofiberscope AF type 22A, Olympus, Tokyo, Japan) could be inserted. With the tip of the fibrescope located between the second and third bifurcation of the right lung, bronchial cross-sectional area was monitored continuously. In addition, a pulmonary arterial catheter was inserted via the femoral vein to allow infusion of lactate Ringer's solution at 4 ml kg$^{-1}$ h$^{-1}$ and for drug administration. Systemic arterial pressure was monitored directly via the femoral artery.

### AIRWAY ANALYSIS

The lungs were ventilated with a respirator

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(Newport ventilator model E-200, Tokibo, Tokyo, Japan) set as follows: $F\text{I}_{\text{O}_2} = 1.0$, controlled mechanical ventilation, ventilatory frequency 10 bpm, I:E ratio 1:1 and end-inspiratory plateau time 0.9 s, and constant inspiratory flow was adjusted to maintain an end-tidal carbon dioxide concentration of 4.5–5.0%. Airway pressure was recorded continuously to calculate dynamic pulmonary compliance and airway resistance. Dynamic pulmonary compliance and airway resistance are reported as the mean value of three consecutive breaths. Bronchial cross-sectional area (as seen by the bronchoscope) at the second–third bifurcation was monitored continuously. The bronchial cross-sectional area image on the monitor was printed via a videoprinter (Videoprinter VY-170, Hitachi, Tokyo, Japan) and measured using image analysis software (NIH image program which is well established and used widely; written by Wayne Rasband at the US National Institutes of Health and available from the Internet by anonymous ftp from zippy. nimh. nih. gov. or on floppy disk from NTIS, 5285 Port Royal Rd., Springfield, VA 22161, part number PB93-504868).

The dogs were allocated to one of two groups: adrenaline–histamine group ($n$=6) and atropine group ($n$=4). In the adrenaline–histamine group, bronchoconstriction was induced with histamine 10 μg kg$^{-1}$ i.v. followed by infusion of 500 μg kg$^{-1}$ h$^{-1}$ via the pulmonary arterial catheter. Systolic arterial pressure was maintained greater than 80 mm Hg with fluid (lactate Ringer's solution 50 ml kg$^{-1}$) and with continuous infusion of phenylephrine 0.5–2.0 μg kg$^{-1}$ min$^{-1}$, the rate being dependent on systolic arterial pressure. Thirty minutes later, when stable bronchoconstriction was achieved, adrenaline was given i.v.: 0 (0.9% saline), 0.05, 0.1, 0.2 and 0.4 μg kg$^{-1}$. The first measurement of dynamic pulmonary compliance and airway resistance was performed before insertion of the fibrescope. Bronchial cross-sectional area, dynamic pulmonary compliance and airway resistance were measured before and 30 min after the start of infusion of histamine and 1 min after each dose of adrenaline. At least 5 min elapsed between each dose of adrenaline. Measured bronchial cross-sectional area, dynamic pulmonary compliance and airway resistance were also expressed as a ratio of basal values (percentage bronchial cross-sectional area, percentage dynamic pulmonary compliance and percentage airway resistance, respectively). In the atropine group, bronchoconstriction was not induced. Thirty minutes after fixation of the bronchoscope, 0.9% saline and 10 min later atropine 0.1 mg kg$^{-1}$ were administered i.v. Only bronchial cross-sectional area was measured before and 5 min after saline and atropine to determine if pentobarbitone anaesthesia reduced bronchial calibre, as seen with thiopentone anaesthesia.[5]

## DATA ANALYSIS

All data are expressed as mean (SD). The correlations between percentage bronchial cross-sectional area and percentage dynamic pulmonary compliance and between percentage bronchial cross-sectional area and percentage airway resistance were calculated by computer assisted curve fitting (Graphpad-Prism). Data were analysed by repeated-measures ANOVA followed by the Scheffé $F$ test. $P<0.05$ was considered significant.

In the adrenaline–histamine group, fibrescope insertion produced no significant change in airway resistance (40.0 (12.4) to 39.1 (11.6) cm $H_2O$ litre$^{-1}$ s$^{-1}$) or dynamic pulmonary compliance (32.0 (12.5) to 32.1 (12.6) ml cm $H_2O^{-1}$). Histamine decreased percentage bronchial cross-sectional area by 49.2 (11.5) %, reduced dynamic pulmonary compliance from 32.1 (12.6) to 22.3 (5.2) ml cm $H_2O^{-1}$ (percentage dynamic pulmonary compliance by 25.2 (7.8) %) and increased airway resistance from 39.1 (11.6) to 57.2 (10.2) cm $H_2O$ litre$^{-1}$ s$^{-1}$ (percentage airway resistance to 153.4 (12.7) %). Adrenaline produced a dose-dependent increase in percentage bronchial cross-sectional area and percentage dynamic pulmonary compliance and a decrease in percentage airway resistance (fig. 1A). There was a significant correlation (fig. 1B) between percentage bronchial cross-sectional area and percentage

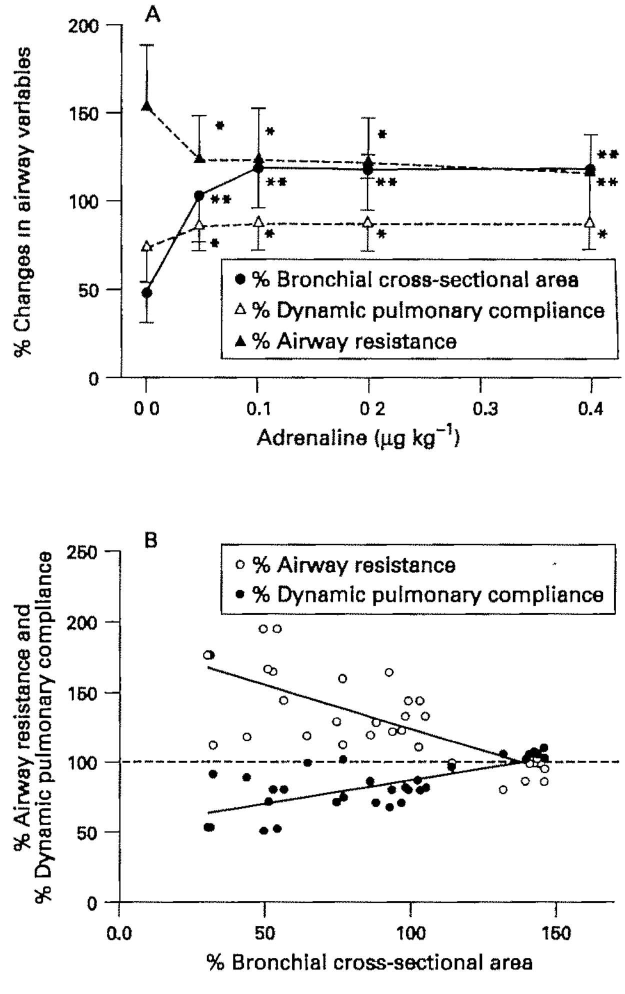

*Figure 1* A: Bronchoconstriction induced by infusion of histamine 10 μg kg$^{-1}$ i.v. and 500 μg kg$^{-1}$ h$^{-1}$. Changes in percentage bronchial cross-sectional area, percentage airway resistance and percentage dynamic pulmonary compliance. Data are mean, SD ($n$=6). $^*P<0.05$, $^{**}P<0.01$ compared with adrenaline 0 μg kg$^{-1}$. B: Correlation between percentage bronchial cross-sectional area and percentage dynamic pulmonary compliance ($r$=0.720, $P<0.0001$) and percentage airway resistance ($r$=0.727, $P<0.0001$).

dynamic pulmonary compliance ($r$=0.720, $P$<0.0001) and percentage bronchial cross-sectional area and percentage airway resistance ($r$=0.727, $P$<0.0001). When these correlations were analysed separately for each subject, the correlation was improved ($r$=0.889 (0.021) and $r$=0.906 (0.044), respectively). In the atropine group, atropine 0.1 mg $kg^{-1}$ produced a significant increase in basal bronchial cross-sectional area to 137.5 (13.8) % ($P$<0.05) compared with bronchial cross-sectional area after administration of 0.9% saline (100.7 (9.8) %).

## Comment

In this study we have reported a new direct method for assessment of airway calibre using a superfine fibreoptic bronchoscope and compared this with conventional indirect measures of dynamic pulmonary compliance and airway resistance. We reported a good correlation between percentage bronchial cross-sectional area, percentage dynamic pulmonary compliance and percentage airway resistance and suggest that our method provided simple, accurate and direct measurement of airway calibre. Calculation of dynamic pulmonary compliance and airway resistance requires airway pressure and pressure gradient measurements, which are dependent on airway smooth muscle tone, presence of oedema, secretion and airflow rate and pattern. Histamine-induced bronchoconstriction, used in this study, produces not only airway smooth muscle contraction and oedema but also an increase in airway secretion[6] which would strongly affect airway pressure measurements but have little effect on airway calibre. Therefore, dynamic pulmonary compliance and airway resistance do not accurately reflect airway calibre.

In support of this notion Brown and colleagues,[4] using high resolution computed tomography, reported that changes in airway calibre did not always follow changes in total pulmonary resistance. Our data also suggested that direct assessment of airway calibre using a superfine fibreoptic bronchoscope was more sensitive than dynamic pulmonary compliance and airway resistance. In histamine preconstricted airways, adrenaline produced greater bronchodilatation than that observed before histamine administration when assessing percentage bronchial cross-sectional area, yet percentage dynamic pulmonary compliance and percentage airway resistance did not completely return to pre-histamine values. These finding were not unexpected. As described above, infusion of histamine increases not only airway smooth muscle tone but also airway secretion. Even if adrenaline completely reversed smooth muscle contraction, airway secretions cannot be excluded. Therefore, dynamic pulmonary compliance and airway resistance would not return fully to basal as airway secretions were not aspirated during the experiment. In addition, our data suggest that pentobarbitone anaesthesia may increase vagal tone to reduce airway calibre as atropine increased basal bronchial cross-sectional area to approximately 140%. Similar data have been reported by Brown and colleagues[5] for thiopentone where atropine 0.2 mg $kg^{-1}$ caused significant airway dilatation (151 (25) %).

In this study, phenylephrine (an $\alpha_1$-agonist) was given i.v. at 0.5–2.0 $\mu g\ kg^{-1}\ min^{-1}$ to maintain systolic arterial pressure greater than 80 mm Hg. When the effect of phenylephrine on histamine-induced bronchoconstriction in dogs ($n$=6) was studied previously, we found that phenylephrine 100 $\mu g\ kg^{-1}$ significantly increased histamine bronchoconstriction while phenylephrine 1.0 and 10 $\mu g\ kg^{-1}$ did not (unpublished data). Therefore, the dose of phenylephrine we used did not significantly affect histamine-induced bronchoconstriction.

## Acknowledgement

We thank Dr D. G. Lambert (University Department of Anaesthesia, Leicester Royal Infirmary, UK) for advice.

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*British Journal of Anaesthesia* 1997; 78: 586–587

# Cardiovascular effects of an intubating dose of rocuronium 0.6 mg $kg^{-1}$ in anaesthetized patients, paralysed with vecuronium

J. M. K. H. WIERDA, M. SCHURINGA AND L. VAN DEN BROEK

## Summary

We have studied, in adult patients, ASA I–II, the cardiovascular effects of an intubating dose of rocuronium 0.6 mg $kg^{-1}$. After induction, patients were paralysed with vecuronium and the trachea intubated. Heart rate (HR) and non-invasive mean arterial pressure (MAP) were measured every 1 min. After stabilization of HR and MAP, defined as <3% change over three measurements, rocuronium ($n$=20) or saline ($n$=10) was injected at random. Mean HR increased initially from 66.6 to 72.1 beat $min^{-1}$, 4 min after rocuronium, and then decreased gradually to 69.6 beat $min^{-1}$, that is a net increase of 3.3 beat $min^{-1}$ over 10 min ($P$<0.001), whereas after saline there was a gradual decrease from 65.8 to 60.9 beat $min^{-1}$ ($P$<0.001) over 10 min. From the third minute, HR was significantly higher in the rocuronium group. Mean MAP decreased in both groups within 10 min to a similar extent after rocuronium and saline, that is from 74.9 to 72.1 mm Hg and from 74.7 to 72.2 mm Hg, respectively (both $P$<0.001). There were no differences in MAP at any time between the rocuronium and saline groups. We conclude that an intubating dose of rocuronium, in the absence of haemodynamic effects related to paralysis itself, resulted in a limited increase in HR without change in MAP, probably because of its weak vagolytic activity. (*Br. J. Anaesth.* 1997; **78**: 586–587).

**Key words**
Neuromuscular block, rocuronium. Neuromuscular block, vecuronium. Cardiovascular system, effects. Intubation tracheal.

Rocuronium is a steroidal non-depolarizing neuromuscular blocking agent with a time course similar to that of vecuronium, but with a faster onset of action. In the cat, rocuronium has a lower vagal: neuromuscular blocking ratio than vecuronium,[1] which may be (partly) responsible for the haemodynamic effects reported in humans.[2–4] An indirect, relaxation-induced reduction in preload caused by abdominal pooling may also contribute to the haemodynamic effects of neuromuscular blocking agents. We studied the cardiovascular effects of an intubating dose of rocuronium in anaesthetized, paralysed patients, to exclude interference from neuromuscular block-induced haemodynamic effects.

## Methods and results

After approval of the local Ethics Committee and with informed consent, we studied 30 ASA I–II patients (aged 18–65 yr), undergoing elective surgery. Patients with neuromuscular or cardiovascular disease and those receiving any potentially interacting medication were excluded. After premedication with oral midazolam 0.1–0.15 mg $kg^{-1}$, anaesthesia was induced with thiopentone 4–6 mg $kg^{-1}$ i.v. and fentanyl 1–3 μg $kg^{-1}$ i.v., and maintained with 1% end- tidal isoflurane concentration and 65% nitrous oxide in oxygen. Tracheal intubation was performed 3 min after vecuronium 70 μg $kg^{-1}$. Heart rate (HR) and mean arterial pressure (MAP) were monitored non-invasively from induction at 1-min intervals. Oxygen saturation was measured continuously, end-expiratory carbon dioxide was maintained at 4.0–4.5 kPa and neuromuscular block was monitored by accelerometry (train-of-four ratio, TOF-Guard). After stabilization of HR and MAP, a bolus of rocuronium 0.6 mg $kg^{-1}$ ($n$=20) or 0.9% saline ($n$=10) was administered over 10 s into a forearm vein according to a randomization scheme. Stability was assumed if <3% change in HR and MAP had occurred over the last three measurements. Measurements were continued for 10 min in the absence of surgical stimulation and HR and MAP were compared within each group (ANOVA for multiple measurements) and between groups (Student's $t$ test for independent samples).

All patients were classified as ASA I. Groups (rocuronium *vs* control) were comparable in age (mean 37.5 (range 20–63) *vs* 34.5 (25–56) yr), height (mean 179 (SD 10) *vs* 178 (7) cm), weight (76.5 (10.3) *vs* 76.1 (10.5) kg) and sex distribution (M/F: 15/5 *vs* 6/4). The interval between intubation and stabilization was 12–16 min. At the time of administration of rocuronium or saline, all patients showed >95% neuromuscular block.

HR and MAP values were similar in both groups

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*Table 1* Heart rate (HR) and mean arterial pressure (MAP) just before (0 min), and for 10 min after a bolus dose of rocuronium 0.6 mg $kg^{-1}$ ($2\times ED_{90}$) or saline (0.9% NaCl) to anaesthetized, paralysed patients. Values are mean (SD) and *P* values are for comparisons between the rocuronium and saline groups

| | Rocuronium ($n$=20) | | Saline ($n$=10) | | |
|---|---|---|---|---|---|
| Time (min) | HR (beat $min^{-1}$) | MAP mm Hg | HR (beat $min^{-1}$) | MAP mm Hg | *P* HR/MAP |
| 0 | 66.6 (11.0) | 74.9 (8.2) | 65.8 (10.4) | 74.7 (10.3) | |
| 1 | 72.0 (11.8) | 76.1 (7.5) | 64.6 (9.4) | 73.6 (10.4) | 0.08/0.51 |
| 2 | 71.5 (11.1) | 74.6 (6.9) | 64.0 (9.5) | 73.3 (10.8) | 0.07/0.74 |
| 3 | 71.9 (11.0) | 73.7 (7.9) | 63.5 (9.6) | 72.3 (11.0) | 0.04/0.74 |
| 4 | 72.1 (10.8) | 73.0 (7.3) | 62.6 (9.6) | 72.0 (10.6) | 0.02/0.80 |
| 5 | 72.0 (10.6) | 73.0 (8.0) | 62.0 (9.4) | 71.2 (9.8) | 0.02/0.62 |
| 6 | 71.2 (10.6) | 72.4 (7.3) | 61.6 (8.8) | 71.3 (10.8) | 0.02/0.78 |
| 7 | 71.0 (10.7) | 72.3 (7.6) | 60.3 (8.2) | 71.1 (10.4) | 0.01/0.74 |
| 8 | 70.3 (10.6) | 72.3 (7.4) | 60.1 (8.4) | 71.6 (10.0) | 0.01/0.85 |
| 9 | 69.7 (10.4) | 72.3 (7.1) | 60.1 (7.9) | 71.3 (10.6) | 0.01/0.80 |
| 10 | 69.6 (10.2) | 72.1 (7.4) | 60.9 (8.2) | 72.2 (11.0) | 0.02/0.97 |

immediately before administration of rocuronium or saline (table 1). After rocuronium, HR increased significantly ($P<0.001$), whereas after saline a limited, but statistically significant decrease in HR occurred ($P<0.001$). In both groups MAP decreased with time to the same small extent ($P<0.001$). After rocuronium, HR was significantly higher than after saline over the interval from 3 to 10 min, whereas MAP did not differ between the groups (see table 1 for *P* values). At the end of the study all patients in the rocuronium group showed complete block whereas twitch height depression in the saline group was still 93.9 (4.1)%.

## Comment

Although rocuronium has a relatively low vagal:neuromuscular blocking ratio in animals compared with vecuronium,[1] it did not show clinically relevant haemodynamic effects in a dose range up to $3\times ED_{90}$ in humans.[3 4] Our results in paralysed patients are in agreement with earlier findings for the same dose in non-paralysed patients.[3] In contrast, Booth and colleagues[2] found more significant increases (>30%) in HR in humans after a similar dose of rocuronium. However, in the latter study hyoscine, a vagolytic agent, which was given as premedication, may have enhanced the slight vagolytic effect of rocuronium, either by addition or synergism. A clinical study[5] in which these drugs were given in reverse order may support this assumption. Methyl-atropine induced a more pronounced vagolytic effect in the presence of high concentrations of rocuronium, compared with low concentrations. In another clinical study,[6] premedication with atropine i.m. was associated with a lower pre-induction HR, most probably because of vagomimetic activity associated with small doses of atropine. This vagomimetic action disappeared after induction of anaesthesia, resulting in a more pronounced increase in HR in patients premedicated with atropine. These findings[5 6] support the likelihood of a drug interaction being the explanation for the different increases in HR in the current study and in that of Booth and colleagues.[2]

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*British Journal of Anaesthesia* 1997; 78: 588–590

# Changes in extracellular brain ascorbate in rat striatum in response to administration of non-volatile anaesthetic agents

M. MIELE AND M. FILLENZ

## Summary

We used constant potential *in vivo* voltammetry to measure changes in striatal ascorbate in the rat in response to i.p. administration of several non-volatile anaesthetics. Propofol and pentobarbitone, which enhance GABA-mediated neuronal inhibitions, decreased ascorbate current to 27.0 (SEM 7.4) % and 46 (6) % of control, respectively. Chloral hydrate, diazepam alone or with ketamine, and fentanyl–fluanisone with midazolam produced no changes in ascorbate current. (*Br. J. Anaesth.* 1997; **78**: 588–590).

**Key words**
Brain, ascorbate. Anaesthetics i.v. Hypnotics benzodiazepine. Rat. Measurement techniques, voltammetry.

*In vivo* voltammetry has been used extensively to monitor extracellular ascorbate in the brain. The extracellular concentration of ascorbate is 416±66 μmol litre$^{-1}$.[1] There is evidence from several different approaches that changes in neuronal activity are accompanied by changes in the extracellular concentration of ascorbate. There is extensive evidence that increased activity of glutamatergic pathways is accompanied by release of ascorbate.[2]

In this study we have used *in vivo* voltammetry to monitor changes in extracellular ascorbate in the rat striatum in response to i.p. administration of various non-volatile anaesthetic agents in order to test the hypothesis that extracellular ascorbate could be used as an index of the level of neuronal activity.

## Methods and results

A carbon paste electrode was implanted stereotactically in the right striatum of male Sprague–Dawley rats (200 and 300 g) under anaesthesia. Extracellular brain ascorbate was measured using constant potential voltammetry.[3] Experiments were performed 24 h after electrode implantation. Anaesthesia was assessed using palpebral, corneal and withdrawal reflexes. Muscle tone was evaluated by assessing resistance to flexion or extension of the limbs.

Results are given as mean (SEM); *n*=number of observations. Data were compared by Students's *t* test using absolute values.

Basal ascorbate current values were 0.89 (0.80) nA (*n*=21) (range 0.3–1.3 nA). After i.p. injection of saline there was a rapid increase in ascorbate, which returned to control values within 5–10 min (fig. 1A).

Two rats were given propofol 25 mg kg$^{-1}$ i.p. The rats were deeply sedated rather than fully anaesthetized for 45 (2.5) min. Transition from sedation to full recovery was slow. Sedation was accompanied by a decrease to 73.0 (7.4) % (*P*=0.038, *n*=8) of basal ascorbate current (fig. 1B) which showed slow recovery and reached basal values only when animals had recovered fully and resumed their normal behaviour.

Sodium pentobarbitone 40 mg kg$^{-1}$ was given i.p. to three rats. Rats were deeply anaesthetized for 91 (4) min and emerged from anaesthesia very slowly. During anaesthesia the ascorbate current decreased gradually to 54 (6.1) % from a baseline current of 0.84 (0.23) nA (*P*=0.0034, *n*=6) (fig. 1C). The decrease in ascorbate produced by sodium pentobarbitone was significantly greater than that produced by propofol (*P*=0.05, Mann–Whitney *U* test).

Chloral hydrate 400 mg kg$^{-1}$ was given i.p. to two rats. Duration of anaesthesia was 107 (7) min, from which rats emerged rapidly and with little warning. There was no change in ascorbate current throughout the period of anaesthesia (fig. 1D). Fluctuations related to motor activity reappeared when animals were recovered fully and resumed their normal behaviour.

Diazepam 5 mg kg$^{-1}$ was administered i.p. to two rats. The animals remained still and sedated for 20–30 min. Basal ascorbate current remained constant throughout the experiment.

A mixture of fentanyl 0.25 mg kg$^{-1}$–fluanisone 0.8 mg kg$^{-1}$ and midazolam 0.4 mg kg$^{-1}$ produced anaesthesia of 35 (5) min duration with no change in ascorbate current throughout the period of anaesthesia.

Ketamine 100 mg kg$^{-1}$ mixed with diazepam 5 mg kg$^{-1}$ was given i.p. to three rats. Duration of anaesthesia was 28 (1.8) min (*n*=5). There were no significant changes in ascorbate current during ketamine–diazepam anaesthesia.

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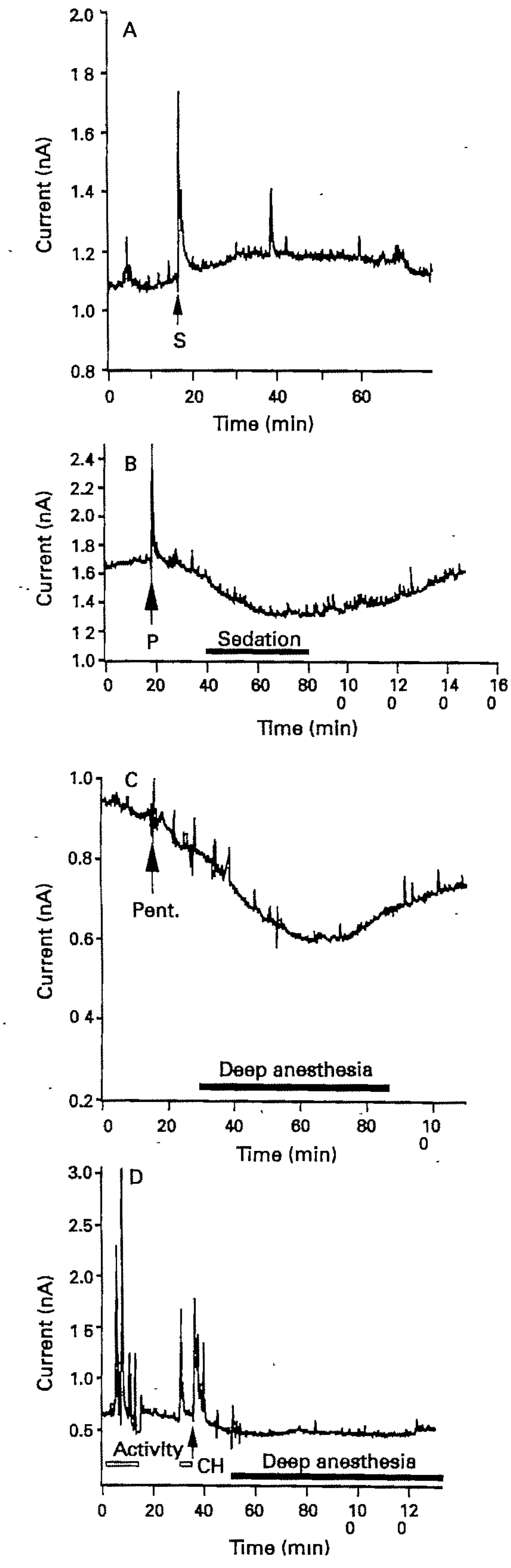

*Figure 1* Ascorbate current recorded from the striatum of a freely moving rat using voltammetry at carbon paste electrodes. A: Effects of saline (S) injection i.p.; B: effects of propofol (P) 25 mg kg$^{-1}$ i.p.; C: effects of pentobarbitone (Pent.) 50 mg kg$^{-1}$ i.p.; D effects of chloral hydrate (CH) anaesthesia 400 mg kg$^{-1}$ i.p. Arrows indicate i.p. injection. Dark bars indicate anaesthesia; white bars indicate spontaneous activity.

## Comment

The results of our experiments, designed to test the hypothesis that extracellular ascorbate could be used as an index of the level of neuronal activity, showed only a partial correlation between reduction in ascorbate current and depth of anaesthesia. Although all drugs produced a significant reduction in behavioural activity and reflex responses, only propofol and pentobarbitone produced a reduction in ascorbate current. These differences are probably a result of different mechanisms of action, although all non-volatile anaesthetic agents reduce the cerebral metabolic demand for oxygen and depress electrophysiological activity. Most anaesthetics either enhance inhibition or depress excitation by interacting with receptors for GABA, glutamate or opioid peptides. A strong correlation exists between drug potency as modulators of the GABA$_A$ receptor and anaesthetic potency *in vivo*.[4]

Propofol and pentobarbitone are lipophilic compounds and act on the GABA$_A$ receptor at a site distinct from that of benzodiazepines, enhancing GABA-mediated transmission.[5] Unlike barbiturates, the benzodiazepines diazepam and midazolam do not directly gate the Cl$^-$ channels of GABA$_A$ receptors but require GABA to express their effects. Voltammetric measurement of ascorbate in a previous study showed that an anxiolytic dose (3 mg kg$^{-1}$) of diazepam had no effect on basal ascorbate current but reduced the stimulated increase in ascorbate.[6] This suggests a different origin for basal and stimulated ascorbate.

Fentanyl mimics the action of opioid peptides acting selectively on μ opioid receptors, which blunt or eliminate responses to noxious stimuli. In microdialysis experiments, fentanyl was found to produce no change in the concentration of glutamate in striatal dialysate (unpublished).

The dissociative anaesthetic ketamine acts on glutamatergic NMDA receptors producing a state of sedation, immobility, amnesia and marked analgesia.

The results of this study suggest that anaesthetic agents which enhance GABA-mediated inhibition of neuronal activity produced a reduction in ascorbate. Although chloral hydrate shares the same mechanism of action as pentobarbitone and propofol, the increase in regional cerebral blood flow and dopamine implies that it produced some neuronal activation.

## Acknowledgements

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*British Journal of Anaesthesia* 1997; 78: 591–593

CASE REPORT

# Conservative management of extradural abscess complicating spinal–extradural anaesthesia for Caesarean section

R. H. DYSART AND V. BALAKRISHNAN

## Summary

We report a case of lumbar extradural abscess that presented 9 days after an elective Caesarean section performed under combined spinal–extradural anaesthesia. This was successfully treated conservatively with full recovery. The clinical course included development, and then resolution, of mild paraparesis. Conservative treatment of an extradural abscess in the obstetric population has not been described previously. (*Br. J. Anaesth.* 1997; **78**: 591–593).

**Key words**
Anaesthesia, obstetric. Anaesthetic techniques, extradural. Anaesthetic techniques, subarachnoid. Complications, extradural abscess.

## Case report

A 26-yr old, 55-kg, para 0, gravida 2 woman presented at 39 weeks' gestation for elective Caesarean section. Indications for surgery were cephalopelvic disproportion and mild pre-eclampsia. A full coagulation screen was not requested as the preoperative platelet count was normal ($178 \times 10^9$ litre$^{-1}$). The obstetric anaesthetic registrar on duty used a combined 16-gauge extradural–spinal pack and 0.5% heavy bupivacaine 3 ml was injected at L3–4 using a 26-gauge pencil point needle; an extradural catheter was then inserted for postoperative pain relief. A routine aseptic technique was used, including gloves, gown, mask, chlorhexidine skin preparation and drapes. Surgery was uneventful and a healthy baby was born with Apgar scores of 9 and 9. No antibiotic prophylaxis was used. At the end of surgery it was noted that blood could be aspirated from the extradural catheter, and therefore the registrar removed it and uneventfully reinserted a new one in a higher space at L2–3. This catheter was used after operation for intermittent top-up doses of extradural pethidine 50 mg in 10 ml saline, administered by the midwife, which was our routine at that time. There was an uneventful postoperative course, the catheter was removed at 48 h (after 13 doses of extradural pethidine), and mother and baby were discharged home after 6 days. There was nothing unusual about the nature of mother's postoperative pain, and she received diclofenac 75 mg once or twice daily while in hospital, and occasional paracetamol.

Late in the evening, 9 days after operation, the woman was readmitted with increasing backache, pyrexia (39.3 °C), white cell count $15.5 \times 10^9$ litre$^{-1}$, erythrocyte sedimentation rate 133 mm h$^{-1}$ and tenderness over the extradural site. There were no signs of endometritis and neurological examination was normal, except for restricted straight leg raising to 70°. She was given opioid analgesia overnight which was effective.

On the following morning she was still pyrexial (39.3 °C) and feeling unwell, with headache and shivering. Her sensation, power and reflexes were still normal, and ceftriaxone, gentamicin and metronidazole were prescribed. After consultation with anaesthetic staff a neurosurgical opinion was obtained. An extradural infection was suspected and conservative treatment was recommended as the patient had no focal neurological signs.

During this 10th day there was worsening of back pain, with pain radiation down both lower limbs, neck pain and headache. PCA morphine was commenced. In the evening she started to develop a vague numb feeling in her right leg, and mild weakness of the left leg. Because of severe back pain when mounting a bedpan, an indwelling catheter was inserted for comfort. Late that evening she felt slightly better with easing of her headache. She had MRC grade 4/5 weakness of ankle flexion on both sides, but there was no impairment of sensation or reflex changes.

The next morning (11 days after operation) she was still pyrexial (39.6 °C) and unwell, with a tachycardia occasionally approaching 150 beat min$^{-1}$. Sensation in her legs was now variable, with patchy numbness to pinprick. Blood cultures obtained on the evening of readmission now revealed gram-positive *Staphylococcus*. At midday she felt reasonably well with a supple neck but with reduced power in all leg muscle groups (4/5) but especially reduced knee extension (1/5). She was photophobic and felt "heavy" in her legs.

The neurosurgeon now considered an MRI scan was indicated because of the neurological signs and

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difficulty in determining how much power and sensation changes were caused by high consumption of PCA morphine. Spinal MRI scan demonstrated a lesion posteriorly at L2–3 which was 2.4×1.2 cm. T1- and T2-weighted images suggested space occupying fluid collection and not old bleeding or fibrosis. The extent and loculation of the lesion, together with the clinical findings, supported a diagnosis of extradural abscess.

Although spinal surgery was considered, it was not performed as there was subjective improvement and reasonably mild neurological signs. At this stage she had foot drop and weakness of ankle inversion/eversion, with no detectable ankle reflexes. There was reduced sensation to pinprick from the L5 dermatome to the perianal region.

From this point on she maintained gradual improvement in her clinical state. On day 12 after operation she again felt slightly improved, with no headache and lessening backache. Her blood cultures confirmed *Staphylococcus aureus*, and the antibiotic regimen was changed to flucloxacillin and rifampicin.

Over the next 2 weeks she continued to improve steadily, mobilizing slowly from day 15 after operation and was afebrile on day 17. Morphine PCA was discontinued on day 18 and on day 20 neurological signs had almost returned to normal apart from altered sensation on the soles of her feet. She still had occasional shooting pains in her thighs and calves, and absent ankle reflexes. She was discharged home on day 25 with a 6-week course of oral flucloxacillin, and ongoing physiotherapy.

One month later she had made a full neurological recovery apart from slight L5 numbness on the right, with normal power and reflexes in her lower limbs. She had no further backache and straight leg raising improved to 90°.

## Discussion

In the recent literature there has been an increase in reported extradural infections associated with extradural anaesthesia.[1–5] However, it is not clear if this represents a real increase in incidence (to accompany the more widespread use of extradural anaesthesia) or merely an increase in reporting. This report represents the second case of extradural abscess after extradural anaesthesia in obstetrics at our institution (see NganKee and colleagues[1]) and has led to cessation of our previous policy of intermittent bolus pethidine top-ups by midwives for analgesia after Caesarean section. We were concerned with frequent accessing of the extradural filter for top-ups (up to 14 doses of extradural pethidine often being used), and thus catheters are now removed at the end of surgery after extradural administration of morphine.

The justification for resiting an extradural after completion of Caesarean section for postoperative pain relief may be debated. However, this was occasionally performed at our institution at that time because of postnatal ward staff request as they were so impressed with the analgesia and earlier mobilization it allowed. We are presently looking at reintroducing extradural pethidine for postoperative Caesarean analgesia in a closed sterile patient-controlled extradural analgesic system.

Most reported extradural abscesses have been unrelated to anaesthesia and are associated with older age, immunocompromise, infection, i.v. drug abuse and trauma.[6–10] Magnetic resonance imaging with contrast enhancement is now the diagnostic tool of choice.[11] There is no agreed *management* of choice. Most authors describe surgical drainage and antibiotic treatment.[2 4 7–10] Percutaneous drainage under x-ray control with irrigation has also been described, although this involves the risk of spread of infection.[12] Others have advocated medical treatment in selected patients[6 11 13] (e.g Leys and colleagues[6]: poor surgical risk; extensive abscess along the vertebral canal; minimal or no neurological deficit; complete paralysis >3 days). Del Curling, Gower and McWhorter[7] found that lumbar abscesses did surprisingly well, usually with full neurological recovery (managed with both operative debridement and antibiotics).

There are no studies to recommend one management in comparison with another. The nature of the condition and the small numbers affected does not readily permit a controlled study of therapies. The variable rate of progression of neurological symptoms after presentation of an extradural abscess makes many neurosurgeons uneasy about conservative treatment. Some cases have had precipitous onset of neurological deficit, suggesting mechanical compression alone is not an adequate explanation. Thrombosis or phlebitis and oedema are probably implicated. It is not clear from the literature however if precipitous irreversible deterioration is a feature of lumbar abscess as it may be with thoracic or cervical abscess. Possibly the young, healthy, obstetric population is different and more amenable to conservative management, especially if the abscess is lumbar and neurological examination is normal or only mildly affected. The extradural space enlarges below L1 and an abscess here usually results in cauda equina syndrome rather than spinal cord compression. However, it is considered important to have the following factors present if pursuing medical management: bacteriological diagnosis, ready access to appropriate imaging, neurosurgical back-up and close clinical follow-up.

In summary, this case report described successful conservative management of extradural abscess in an obstetric patient. Such management has been reported previously in other groups of patients, but not in the obstetric population.

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EQUIPMENT

# KTP laser-resistant properties of the reinforced laryngeal mask airway

J. J. PANDIT, P. CHAMBERS AND S. O'MALLEY

## Summary

We have assessed, *in vitro*, the effect of KTP laser strike on the reinforced laryngeal mask airway (RLMA) under a variety of conditions. At power densities normally encountered in clinical practice, using a divergent KTP laser beam, the RLMA could not be penetrated and did not ignite with laser strike. The RLMA was penetrated at a high power density of 6.94 W $mm^{-2}$ after 45–60 s. A flame appeared over the RLMA shaft at this power density after 12–35 s. The black marker line on the RLMA shaft was somewhat more vulnerable to the effects of laser strike. The flow of oxygen and nitrous oxide within the shaft did not appreciably alter the laser-resistant properties of the RLMA. The RLMA cuff was more vulnerable to laser strike than was the shaft and was penetrated at very low power densities. Filling the cuff with saline had a protective effect and penetration did not occur at power densities which caused penetration of air-filled cuffs (0.37 W $mm^{-2}$). (*Br. J. Anaesth.* 1997; **78**: 594–600).

**Key words**
Equipment, lasers. Equipment, masks anaesthesia. Surgery, otolaryngological.

Laser surgery was introduced into otolaryngology in the early 1970s. Strong and Jako first used the carbon dioxide laser in laryngeal work.[1] Since then the use of the laser has become widespread. The carbon dioxide laser is delivered by a bulky articulated arm or by coupling to an operating microscope. These delivery methods limit the manoeuvrability and access to tissue that the surgeon can achieve.

The Nd:Yag laser (yttrium-aluminium-garnet treated with neodymium ions pumped with a krypton arc lamp) was introduced in the 1980s.[2] Its main advantage over the carbon dioxide laser is that it can be delivered by means of a more easily handled fibreoptic light cable. It has greater coagulative properties but less cutting ability than the carbon dioxide laser. Du Pont introduced the KTP laser in the 1980s. This laser uses an Nd:Yag laser to produce a beam at a wavelength of 1064 nm which is then passed through a potassium titanyl phosphate (KTP) crystal to produce visible green light at a wavelength of 532 nm.[2] This light can be transmitted through a fibreoptic cable, producing a divergent beam, or through an operating microscope producing a coherent (parallel) beam. A divergent beam diffuses its energy over a progressively wider area as it travels away from the source, whereas a parallel beam imparts its total energy over the same area whatever the distance of the source from the target. Therefore, parallel KTP or carbon dioxide laser beams impart much higher power densities to the tissues they strike than does the divergent KTP laser. The KTP laser cuts better and faster than the Nd:Yag and coagulates better than the carbon dioxide laser.[2 3] Tissues can therefore be cut, coagulated and vaporized with the same laser by varying power, exposure time and spot size. Unlike the Nd:Yag laser which needs an expensive shaped sapphire tip to produce good cutting, the KTP can achieve this using a bare fibre.

The KTP laser is now used extensively in ENT surgery for stapedectomy, tympanoplasty, reduction of turbinates and in functional endoscopic sinus surgery. Its greatest use is probably in oropharyngeal surgery in resecting tissue and in laryngeal work where its vaporizing properties are more useful.[3–5]

During laser surgery of the oral or laryngeal cavities, there is a serious risk of ignition of the tracheal tube.[6] To avoid laser fire, special anaesthetic techniques and tracheal tubes have been designed, and several studies have examined the laser-resistant properties of such tracheal tubes.[7–10]

Although the laryngeal mask airway (LMA) and the reinforced laryngeal mask airway (RLMA) are being used increasingly during laser surgery of the upper airway,[11] there have been relatively few reports of their laser-resistant properties. Brimacombe and co-workers have reported on the incendiary properties of the RLMA to carbon dioxide lasers[12 13] and found that it is resistant to penetration, ignition and combustion compared with PVC tracheal tubes.

To our knowledge, the incendiary characteristics of the RLMA to the KTP laser have not been studied previously. The main aim of this study was to assess if the RLMA is resistant *in vitro* to penetration and combustion using a divergent beam, at power densities normally encountered in our standard surgical practice. Second, we wished to determine the power density at which the RLMA would be penetrated or ignite.

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## Materials and methods

### LASER SOURCE

A Laserscope KTP surgical laser system (Laserscope Inc, San Jose, CA, USA) was used to deliver the laser beam via a Laserscope Endostat optical delivery fibre (0.3 mm radius). This is a quartz thread covered by silicone cladding and a plastic–silicone jacket. The purpose of the cladding is to reflect light travelling within the fibre, and the jacket offers mechanical support. Before each experiment, the fibre was stripped and calibrated in accordance with the manufacturer's instructions. The power output at source of the Laserscope surgical delivery system could be varied between 0 and 20 W.

The laser beam is divergent around the fibre core at 15° (that is 7.5° each side of the core). The fibre radius is 0.3 mm, so the area of laser strike at a distance $d$ and thus the power density of the laser strike on the laryngeal mask is in accordance with equations (1–3) (personal communication, Rhys Llewellyn, European Marketing Manager, Laserscope):

$$\text{Power density (W mm}^{-2}) = \text{power output of laser at source (W) / area of laser strike (mm}^2) \quad (1)$$

$$\text{Area of laser strike} = \pi(0.3+x)^2 \quad (2)$$

$$x = d(\tan 7.5°) \quad (3)$$

Therefore, on contact of the fibre with the shaft, the area of laser strike is 0.28 mm$^2$; at a distance of 5 mm, the area is 2.88 mm$^2$.

### LARYNGEAL MASK AIRWAY

A set of RLMA (Intavent Ltd, Reading, UK) of standard dimensions were used: size 2.5, mean wall thickness 1.7 mm (range 1.55–1.85 mm; tolerance ±0.15 mm) and cuff wall thickness 0.55 mm (range 0.45–0.65 mm; tolerance ±0.1 mm). Each RLMA was labelled with its own identifying number (e.g. 031, 032, etc).

### EXPERIMENTAL DESIGN

Each procedure was conducted under the same experimental design. The RLMA was held steady by a metal clamp on a metal stand. Gas flow through the RLMA was provided by attaching it to a standard co-axial breathing system from a Boyle's machine. The laser-emitting fibre was held in place by a metal clamp on a second metal stand, allowing the distance ($d$) between the fibre and RLMA to be adjusted (eqn (3)). The laser beam was directed to the clear part of the shaft, between the metal rings. This was because the total area presented by the metal rings is relatively small and it was felt that under clinical conditions a laser would be more likely to involve the clear part of the tube. The metal rings were struck by the laser when the diameter of the area of laser strike exceeded the distance between the metal rings (i.e. greater than 1 mm). In each procedure, laser strike was continued either for a preset period of time (e.g. 20 s) or until an effect on the RLMA was seen. Video recordings of the experiments were made and any significant effects and the time at which they occurred were recorded.

The experimental procedures were designed to examine a sequence of questions.

### EXPERIMENTAL PROCEDURES

*Procedure A: at a power density normally encountered in standard practice, do different RLMA have similar laser-resistant characteristics?*

This was the control to establish that the supply of RLMA was homogeneous. The RLMA was held free-standing in room air not attached to the anaesthetic system. Using a laser source power output of 10 W, the fibre was held at a distance of 5 mm from the shaft (power density 3.47 W mm$^{-2}$). Laser strike was maintained continuously for 20 s. A total of seven separate tubes were used, and each tube was subjected to at least two exposures at this power density.

*Procedure B: what is the effect of increasing the power density by reducing the distance between the laser fibre tip and the RLMA shaft?*

RLMA were held free-standing in room air. A laser source power output of 10 W was selected and laser strike was maintained continuously for 20 s. Tests were conducted at distances between the RLMA and laser fibre of 5 mm (power density 3.47 W mm$^{-2}$), 3 mm (power density 6.57 W mm$^{-2}$), 2 mm (power density 10 W mm$^{-2}$) and with the fibre in contact with the RLMA (power density 35.7 W mm$^{-2}$).

*Procedure C: what is the effect if the laser strikes the radio-opaque black marker line on the RLMA shaft?*

The RLMA was held free-standing in room air. A laser source power output of 10 W was selected with the fibre at a distance of 5 mm from the shaft (power density 3.47 W mm$^{-2}$). Laser strike was maintained continuously for 20 s with the laser aimed at the black line on the RLMA shaft.

*Procedure D: does oxygen and nitrous oxide flow within the RLMA have any effect on the laser-resistant properties of the shaft?*

A laser source power output of 10 W was selected, the fibre at a distance of 5 mm from the RLMA shaft as in experimental procedure A (power density 3.47 W mm$^{-2}$). The RLMA was attached to the anaesthetic system with a flow of oxygen 2 litre min$^{-1}$ and nitrous oxide 4 litre min$^{-1}$. Laser strike was maintained continuously for 20 s.

*Procedure E: at what power density can the RLMA be penetrated or ignite?*

Three separate groups of experiments (E1, E2 and E3) were performed.

*Experiment E1 (effect of increasing power output at a fixed distance).* The RLMA was connected to the anaesthetic system with oxygen 2 litre min$^{-1}$ and nitrous oxide 4 litre min$^{1}$ flowing through it. The laser fibre was held at a distance of 5 mm from the shaft. Laser strike was continuous for up to 60 s. The effects of power outputs of 10 W (power density 3.47 W mm$^{-2}$), 15 W (power density 5.21 W mm$^{-2}$) and 20 W (power density 6.94 W mm$^{-2}$) were observed.

*Experiment E2 (effect of increasing power output with laser fibre in contact with RLMA).* The RLMA was connected to the anaesthetic system with oxygen 2 litre min$^{-1}$ and nitrous oxide 4 litre min$^{1}$ flowing through it. The laser fibre was held in contact with the RLMA shaft and laser strike was continuous until an effect was observed. The effects of power outputs of 10 W (power density 35.7 W mm$^{-2}$) and 20 W (power density 71.4 W mm$^{-2}$) were noted. The laser fibre was pushed through the damaged RLMA and 20 W of power reapplied with oxygen and nitrous oxide flowing through the system and RLMA shaft.

*Experiment E3 (effect of oxygen and air mix flowing through the RLMA).* The RLMA was connected to oxygen 2 litre min$^{-1}$ and air 4 litre min$^{-1}$ flowing through the anaesthetic system. The laser fibre was held in contact with the RLMA shaft and a power output of 20 W was applied (power density 71.4 W mm$^{-2}$). After 45 s the laser fibre was pushed through the damaged RLMA and the power output of 20 W was reapplied to assess the effects of laser within the oxygen and air gas stream.

### *Procedure F: what is the effect of the laser on the RLMA cuff filled with air?*

The RLMA was held in its clamp, free-standing in room air. The laser power output at source was set to 10 W. The RLMA cuff was filled with 12 ml of air, in accordance with the manufacturer's instructions. First, the laser fibre was held 10 mm from the cuff (power density 1.22 W mm$^{-2}$) and laser strike was continued for 20 s. Second, the laser fibre was held 20 mm from the cuff (power density 0.37 W mm$^{-2}$) and laser strike continued for 20 s. Third, the fibre was held 35 mm from the cuff (power density 0.13 W mm$^{-2}$) and laser strike was continued for 60 s. Finally, the fibre was held 40 mm from the cuff (power density 0.10 W mm$^{-2}$) and laser strike continued for 60 s.

### *Procedure G: what is the effect of the laser on the RLMA cuff filled with saline?*

The RLMA was held in its clamp, free-standing in room air. The laser power output at source was set to 10 W. The cuff was filled with 12 ml of saline. First, the laser fibre was held 10 mm from the cuff and laser strike continued for 20 s (power density 1.22 W mm$^{-2}$). Second, the fibre was held 20 mm from the cuff and laser strike continued for 60 s (power density 0.37 W mm$^{-2}$).

## Results

The result of procedure A was that there was no discernible effect of laser strike on the clear part of the shaft after continuous firing for 20 s.

In procedure B (table 1), there was no penetration of the shaft with the laser strike, even at relatively high power densities. At a power density of 10 W mm$^{-2}$ the surface silica layer gave a yellow–green "flare" within 7 s of being struck by the laser, a layer of silica ash then formed which seemed to prevent further penetration of the shaft by the laser beam. Higher power densities (35.7 W mm$^{-2}$) caused the surface to flare within 1 s: a flame then burned along the plastic sheath of the laser fibre, but there was no fire on the RLMA and after 20 s there was no penetration of the shaft.

In procedure C (table 2), at a power density (3.47 W mm$^{-2}$) which had no effect on the clear part of the

*Table 1* Experimental procedure B: effect of increasing laser power density on RLMA shaft. RLMA were in room air

| Power density (W mm$^{-2}$) | Power at source (W) | Distance (mm) | Effect after 20 s | No. of separate RLMA tested | Total No. of tests |
|---|---|---|---|---|---|
| 3.47 | 10 | 5 | None | 11 | 11 |
| 6.57 | 10 | 3 | None | 3 | 4 |
| 10.0 | 10 | 2 | 7 s: yellow–green flare<br>20 s: crater in tube wall filled with silica ash—no penetration of shaft | 4 | 6 |
| 35.7 | 10 | Contact | 1 s: yellow–green flare<br>5–6 s: flame spread along plastic sheath of laser fibre (no flame or fire on RLMA)<br>20 s: crater in tube wall filled with silica ash—no penetration of shaft | 8 | 8 |

*Table 2* Experimental procedure C: effect of laser strike on the black line on RLMA shaft. RLMA were in room air

| Power density (W mm$^{-2}$) | Power at source (W) | Distance (mm) | Effect after 20 s | No. of separate RLMA tested | Total No. of tests |
|---|---|---|---|---|---|
| 3.47 | 10 | 5 | 1 s: instant flare<br>20 s: crater filled with silica ash, but no penetration | 5 | 5 |

*Table 3* Experimental procedure D effect of oxygen 2 litre min$^{-1}$ and nitrous oxide 4 litre min$^{-1}$ flow within the tube on the laser-resistant properties of RLMA

| Power density (W mm$^{-2}$) | Power at source (W) | Distance (mm) | Effect after 20 s | No. of separate RLMA tested | Total No. of tests |
|---|---|---|---|---|---|
| 3.47 | 10 | 5 | None | 6 | 6 |

*Table 4* Experimental procedure E: effect of high laser power densities on RLMA. *With laser fibre then pushed through hole made (see text); †oxygen 2 litre min$^{-1}$, nitrous oxide 4 litre min$^{-1}$; ‡oxygen 2 litre min$^{-1}$ and air 4 litre min$^{-1}$

| Power density (W mm$^{-2}$) | Power output at laser source (W) | Distance (mm) | Gas flow within RLMA | Effect | No. of separate RLMA tested | Total No. of tests |
|---|---|---|---|---|---|---|
| Procedure E1 | | | | | | |
| 3.47 | 10 | 5 | $O_2/N_2O$† | No effect after 60 s | 6 | 6 |
| 5.21 | 15 | 5 | $O_2/N_2O$† | No effect after 60 s | 2 | 4 |
| 6.94 | 20 | 5 | $O_2/N_2O$† | See text for description | 1 | 1 |
| Procedure E2 | | | | | | |
| 35.7 | 10 | Contact | $O_2/N_2O$† | See text for description | 1 | 1 |
| 71.4 | 20* | Contact | $O_2/N_2O$† | See text for description | 1 | 1 |
| Procedure E3 | | | | | | |
| 71.4 | 20* | Contact | $O_2$/air‡ | See text for description | 1 | 1 |

shaft (procedures A and B, table 1), laser strike on the black line caused an instant flare and after 20 s produced a crater filled with silica ash. This crater was similar to that produced at a power density of 10.0 W mm$^{-2}$ on the clear part of the shaft (table 1), but subjectively, was somewhat deeper. There was no penetration of the RLMA.

In procedure D (table 3), at a power density of 3.47 W mm$^{-2}$ (which had no effect in experimental procedures A and B), the flow of gases which support combustion within the tube did not change the laser-resistant properties of the shaft.

In procedure E (table 4), the RLMA shaft proved to be laser-resistant up to power densities of 5.21 W mm$^{-2}$ for durations of 60 s.

In procedure E1, at a power density of 6.94 W mm$^{-2}$, a yellow glow and smoke appeared over the surface of the shaft within 12 s, followed shortly by a flame along the laser fibre. At 35 s there was a yellow flame on the shaft; this did not spread away from the point of laser strike. The experiment was stopped after 45 s when a crust of silica ash had formed; this was removed to reveal that the shaft had been penetrated, with the metal rings broken.

In procedure E2, at a power density of 35.7 W mm$^{-2}$, a flame appeared at 10 s spreading along the laser fibre, followed by a glow and a flame localized to the point of laser strike. A crust of silica ash formed. After 60 s when the experiment was stopped, examination revealed that when the crust of ash was removed, the shaft underneath was penetrated and the metal rings broken. At 71.4 W mm$^{-2}$, there was an instant glow followed by a flame which spread over the surface of the shaft. Simultaneously, smoke appeared within the lumen of the shaft. The experiment was stopped at 15 s when there was a spreading fire which was extinguished by a fire extinguisher. When the laser fibre was pushed through the hole in the RLMA, there was a near-instant conflagration with laser strike: the flame burned within the shaft both towards the cuff and retrogradely towards the anaesthetic machine. The cuff exploded with a loud bang. The gas flow was turned off and the fire extinguisher was applied, but despite this, an incandescent glow remained over the surface of the shaft for 45 s.

In procedure E3, at a power density of 71.4 W mm$^{-2}$ with a mixture of oxygen and air flowing within the shaft, there was smoke within the shaft at 10–12 s, followed by a surface yellow flame and yellow glow inside the tube. At 45 s, the experiment was stopped: when the silica crust was removed, the tube was found to have been penetrated and the metal rings broken. Pushing the laser fibre through the hole in the shaft caused an instant glow and a flame at 10 s. It did not result in the conflagration seen when oxygen–nitrous oxide was used.

In procedure F (table 5), the air-filled cuff ruptured within 6 s at power densities as low as 0.37 W mm$^{-2}$ (accompanied by a characteristic "pop" and cuff deflation). Continued firing of the laser (at 1.22 W mm$^{-2}$ for up to 20 s) did not cause the ruptured cuff to ignite. With very low power densities (0.13 W mm$^{-2}$), the area of cuff struck by the laser darkened and slowly formed an "aneurysm": after 60 s of continuous firing, this area was found to be extremely brittle and disintegrated with the slightest manipulation. At the lowest power density (0.10 W mm$^{-2}$ for

*Table 5* Experimental procedure F: effect of laser on RLMA cuff filled with air. RLMA held free-standing in room air

| Power density (W mm$^{-2}$) | Power at source (W) | Distance (mm) | Cuff filled with | Time to penetration (s) | Effect | No. of separate RLMA tested | Total No. of tests |
|---|---|---|---|---|---|---|---|
| 1.22 | 10 | 10 | Air | 1–3 | Rupture | 3 | 3 |
| 0.37 | 10 | 20 | Air | 6 | Rupture | 2 | 2 |
| 0.13 | 10 | 35 | Air | 60 | See text | 1 | 1 |
| 0.10 | 10 | 40 | Air | — | See text | 1 | 1 |

*Table 6* Experimental procedure G: effect of laser on RLMA cuff filled with saline. RLMA held free-standing in room air

| Power density (W mm$^{-2}$) | Power at source (W) | Distance (mm) | Cuff filled with | Time to penetration (s) | Effect | No. of separate RLMA tested | Total No. of tests |
|---|---|---|---|---|---|---|---|
| 1.22 | 10 | 10 | Saline | 5–11 | See text | 3 | 3 |
| 0.37 | 10 | 20 | Saline | — | No effect | 2 | 2 |

60 s), this aneurysmal area formed but was not brittle and did not disintegrate.

In procedure G (table 6), a power density which had caused explosive cuff rupture within 6 s in the air-filled cuff (0.37 W mm$^{-2}$), had no effect after 60 s of continuous firing on the saline-filled cuff. At the highest power density used which had caused explosive rupture of the air-filled cuff within 3 s (1.22 W mm$^{-2}$), the saline-filled cuffs lasted between 5 and 11 s before (non-explosive) penetration caused saline to leak out in a small jet. There was less subsequent deflation compared with the air-filled cuff, as some saline remained in the cuff.

## Discussion

At laser power outputs and at distances of the laser fibre tip from the RLMA normally encountered in clinical practice, the RLMA was not penetrated or ignited by KTP laser strike. While some surface changes did occur, the layer of silica ash which formed appeared to protect the RLMA shaft from further damage (procedure B; table 1). However, the black line and lettering on the RLMA shaft were more vulnerable to the effects of the laser. Longer exposures to laser strike had a detrimental effect: a power density of 6.57 W.mm$^{-2}$ for 20 s had no effect (table 1), but a slightly higher power density of 6.94 W mm$^{-2}$ for 60 s caused shaft penetration (table 4). Similarly, a power density of 35.7 W mm$^{-2}$ for 20 s caused only surface changes (table 1), but after 60 s caused penetration (table 4). The air-filled cuff ruptured rapidly on laser contact at very low power densities; filling the cuff with saline had a protective effect.

Fried, Mallampati and Caminear[10] studied the effects of KTP laser strike on a selection of tracheal tubes. Using only one (extremely high) power density of 250 W mm$^{-2}$ for 60 s, they found the following tubes to ignite within 31 s: unwrapped PVC tubes (Sheridan and Mallinckrodt), unwrapped red rubber tubes (Rusch) and metallic-coated silicone tubes (Xomed Laser Shield). Only red rubber tubes wrapped with aluminium foil and corrugated stainless steel tubes (Mallinckrodt Laser-Flex) were resistant to the laser at this power density (although the silicone-covered corrugated steel tubes (Bivona Fome-Cuff) did suffer surface changes). The power density used in this study was different from that used in our study and direct comparison is therefore difficult, but the fact that red rubber tubes wrapped with aluminium foil and corrugated stainless steel tubes did not ignite suggests that these may be somewhat safer than the RLMA to laser strike. It is interesting that Fried, Mallampati and Caminear[10] also found the black marker line of the tracheal tubes to be less laser-resistant than the shaft.

Brimacombe and colleagues[12 13] tested the incendiary properties of the RLMA to carbon dioxide laser strike, and the results were similar to ours, although the relevant power densities differed with the different laser used. At 23.5 W mm$^{-2}$, the shaft was penetrated after 20–30 s but there was no ignition. Brimacombe and colleagues noted a layer of silica ash sitting on top of the crater, apparently "protecting" the shaft from further penetration or ignition (similar to our results in table 1). However, at very high powers (980 W mm$^{-2}$), the RLMA did ignite almost immediately. The cuff was also found to be less resistant, being penetrated within 5 s, but Brimacombe and co-workers did not test the effect of saline in the cuff or of laser on the black marker line.

Our study was an *in vitro* bench study. In the clinical situation, the risk of flammability may be affected by the presence of surrounding tissue or small particles of blood which may act to absorb laser energy and so cause ignition at lower power densities than the RLMA itself.

Our study provides no direct comparison of the RLMA with tracheal tubes to laser strike. There is controversy as to which tracheal tube is the most laser-resistant and which should ideally be compared with the RLMA.[6–10] Recognizing that RLMA are used by many anaesthetists in laser surgery of the upper airway, our main purpose was to document the laser-resistant properties of the RLMA alone, by using several experimental procedures in repeated studies. Further experiments of a different design are needed to compare the RLMA with tracheal tubes.

Our study was limited in that not every combination of conditions was tested. For example, the black marker line was tested at only one power density (table 2), and the effect of oxygen–nitrous oxide on laser strike on the cuff was not assessed. However, we feel that designing the experimental procedures to answer a sequence of questions enabled us to draw more practical conclusions from the study. For example, we can conclude with confidence that at a power density which does not affect the shaft (table 1), striking the black line increased the vulnerability of the RLMA (table 2); oxygen–nitrous oxide did not have such a marked effect (table 3).

We have attempted to emulate the laser strike which might *normally* occur in clinical practice. We have also been careful to express our results in terms of the incident laser power *density* which we believe is the relevant variable that determines outcome. Some previous studies have not adhered to this approach so rigorously.[6 13] Thus in most of the experiments, submaximal power outputs were used at distances of

2–5 mm from the shaft and 10–20 mm from the cuff. Most other studies also appear to have examined a different question, namely: "Does the RLMA or tracheal tube ignite at all?"[9,10] We do not think that this is a very useful question if the RLMA is then examined at power densities not found in clinical practice. We did, in fact, examine the effects under more extreme conditions and our conclusion does not differ in this respect from that which might be predicted: *virtually any device will ignite or be penetrated if the laser strike is powerful enough.*

Based on our findings, several recommendations may be made on the safe use of the RLMA in the presence of the divergent KTP laser.

(1) The surgeon should clearly exercise caution and avoid direct laser strike on the RLMA shaft or cuff. This risk is minimized if a Boyle–Davis gag without the Doughty modification is used and the gag is opened as widely as possible: in this situation neither the RLMA cuff nor the shaft can be seen.[14] The risk of airway obstruction using an unmodified gag might, however, be high,[15,16] and if this is the case then it would be sensible to use a modified gag and to protect the RLMA shaft by covering the slit with a dampened gauze or swab. The power output used should be the minimum required and laser duration should be limited. In this way, the risk of penetration of the shaft by the laser (which occurred in this study after 45–60 s at a power output of 6.94 $\mathrm{W\ mm^{-2}}$ and higher; table 4) is minimized.

(2) Consideration should be given by the manufacturers to produce RLMA in which there is no black marker line or lettering, or in which this is placed much higher up the shaft than it is at present. The purpose of the lettering is to identify the device as an RLMA (probably unnecessary), but more importantly, to identify its size. The purpose of the black line is to identify the midline of the shaft: when the device is inserted, this line should ideally be central and point cranially. It might at first be thought that this line serves a very important function. However, in a *reinforced* laryngeal mask, which has a flexible shaft, the portion of the shaft and so also the black line lying *outside the mouth* varies considerably and as such cannot accurately indicate the way in which the shaft or cuff is lying *inside the mouth*. The benefits of retaining the black line and lettering appear to be outweighed by the reduced ability of the RLMA to resist laser strike (table 2). Therefore, it is our contention that, for use with laser surgery to the head and neck, RLMA without the black line should be used.

(3) This study lends no direct support to the notion that the use of gases which support combustion (i.e. oxygen and nitrous oxide) markedly reduced the laser-resistant properties of the RLMA (table 3). It is clear that under some, extreme circumstances ignition can occur and it would therefore be prudent to consider using only air–oxygen mixtures rather than oxygen–nitrous oxide during maintenance of anaesthesia, unless there is a compelling reason to use nitrous oxide.

(4) The cuff is more vulnerable to laser strike than the shaft (table 5). Filling the cuff with saline affords protection and therefore is the safe method in the presence of lasers. Consideration might also be given to the use of methylene blue or a coloured inert indicator so that the operator knows if the cuff has ruptured. The disadvantages of using saline in the cuff are that the manufacturers only recommend filling the cuff with air and as not all of the saline can be withdrawn from the cuff after use, this may cause cuff rupture during autoclaving.[17] The cost–benefit balance of using saline thus remains to be determined.

(5) With the increasing use of lasers in clinical practice and especially with regard to tubes marketed specifically for use in laser surgery, it would be desirable that in future, manufacturers tested for and published tolerance levels of their devices to laser strike from a variety of lasers at different power densities.

## Acknowledgements

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COMMENTARIES

# Calculation of drug dosage and body surface area of children

J. A. LACK AND M. E. STUART-TAYLOR

## Summary

The *British National Formulary* and many reference textbooks recommend that drug dosages for children be calculated according to body surface area (BSA). Although many rules for drug dosage have been developed, based on age, weight and surface area, none has been accurate and simple enough for routine use. These rules are described, and one for clinical use: up to 30 kg, a child's drug dose may be (wt x 2)% of an adult dose; over 30 kg, (wt+30)% of an adult dose. If this percentage of an "adult" dose of a drug is used, not only is the BSA curve followed more closely than with the conventional mg $kg^{-1}$ regimen, but fewer major errors of prescription may be expected. (*Br. J. Anaesth.* 1997; **78**: 601–605).

**Key words**
Anaesthesia, audit. Children. Anaesthesia, administration schedule

The *British National Formulary* (*BNF*),[1] *Martindale's Pharmacopoea*[2] and many other reference textbooks state that the most reliable methods for calculation of children's drug doses are those based on body surface area (BSA). This principle has been commended for nearly 90 yr, but there is still no consistency in the guidance offered, and the same *BNF* uses a mixture of mg $kg^{-1}$, age and weight ranges in its recommendations.

All dosage rules based on a single physical dimension only hold good while that dimension is associated with other normal dimensions. Thus one could use an age-based rule if associated height and weight for that age were typical; however, there is substantial normal variation in height and weight with age (see below) and so weight is used more usually as the dimension for calculations. This however is still relatively unreliable, and therefore if better prediction of drug concentrations is required, a multidimensional rule is needed. Fortunately, this is usually beyond clinical needs.

The therapeutic ratio (the ratio of toxic to effective dose) for most drugs is more than 50%, so that some approximation may usually be made with safety. It would appear that for routine practice, an "accuracy" of 10–20% is reasonable; more than this complicates the mathematics substantially, and would not be justified because of individual differences in response. This generalization excludes those drugs which are given according to known individual requirements (e.g. insulin or digoxin), for which a prescribing rule is inappropriate.

A large number of children's drug dosage rules have been described,[3–5] almost all using percentages of an adult dose to calculate an appropriate child's dose—the notable exception being the commonly used "*n*" mg $kg^{-1}$ regimen. An advantage of these rules is that modifications to adult doses to allow for sickness in adults are appropriately incorporated into calculations for children. An obvious requirement of these percentage methods is that adult doses of the drug are known, but for the majority of anaesthetists this does not present a problem, and certainly no more difficulty than the different dosages at different ages noted in the *BNF*.

Reports in the literature quote many examples of prescription errors in children, of 2–10 times the recommended dose.[6–10] Many believe that the great majority of these errors would have been noticed if easily calculated percentages of a normal adult dose had been used, as the prescriber may readily check his mathematics by inspection of the values involved.

Dosage rules may be described as those based on age, weight or body surface area.

## Age-based rules

The earliest rules used age as the base. Augsberger[3] referred to Dilling's rule (age/20) as dating back to

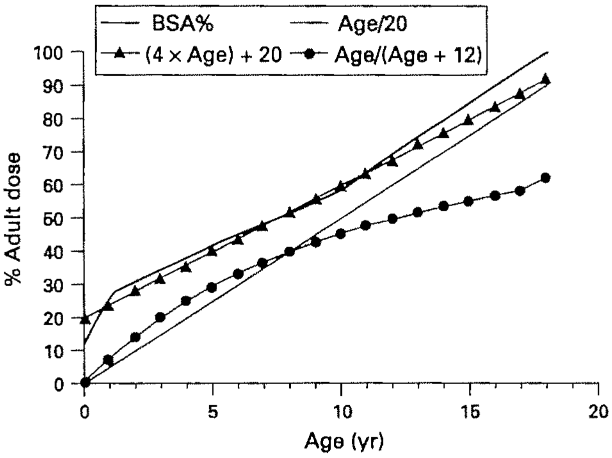

*Figure 1* Age-based rules at ages shown for calculation of childrens' drug dosages as a percentage of adult doses plotted using weights derived from standard growth tables

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the 8th century. Those most commonly used:

age/20, (4×age)+20 and age/(age+12)

are shown in figure 1, plotted using weights for ages obtained from standard tables.[11 12] The normal variation of weight with age (from 3rd to 97th percentiles) is considerable, being least at 1 yr (+25% to −20% at 10 kg), and reaching a maximum at about 13 yr (+45% to −26% at 40 kg). The consequence is that these rules are highly unreliable.

If weight is unavailable, then (4×age)+20 provides the best fit to the BSA curve for normal sized children.

## Weight-based rules

Professor A. J. Clark of Edinburgh is said to have been the first to propose a weight proportional regimen for drug therapy.[13] His first rule was:

(wt (lb)/150) fraction of an adult dose.

This was improved in accuracy by Augsberger,[3] who substituted multiplication for division and added 10, suggesting:

((1.5×wt (kg))+10) percent of an adult dose.

However, this made it difficult to calculate, and this rule is not quoted widely. It is as good a linear fit as can be made to the BSA curve, reaching 100% at 60 kg (fig. 2).

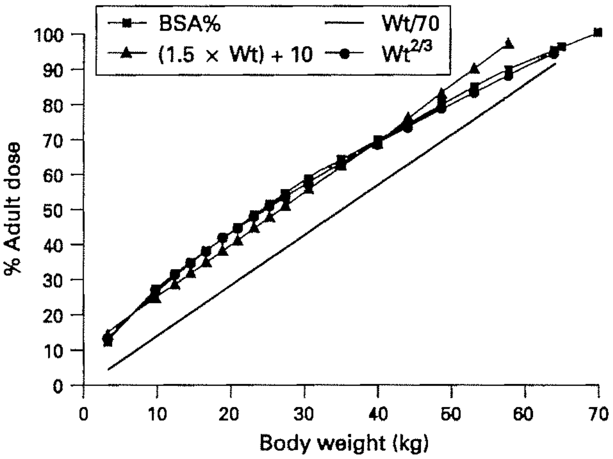

*Figure 2* Weight-based rules for calculation of childrens' drug dosages as a percentage of adult doses.

The most common regimen, mg kg$^{-1}$ dosages, has an attractive simplicity which has given it widespread popularity despite its disadvantages, namely: (a) it requires a complete set of drug dosages ($n$ mg kg$^{-1}$) to be learned for its purpose, and indeed different doses at different ages[1]; (b) the mathematics may not be as easy as a bedside rule demands, the decimal point sometimes being misplaced when tenths or hundredths of a mg kg$^{-1}$ are being multiplied; (c) it does not immediately relate to adult doses, so that inappropriate prescriptions are not immediately obvious; (d) assays of drug concentrations show that its use "under doses" for much of its range[14]; this varies from approximately −45% at 15 kg to −20% at 40 kg compared with the BSA graph (fig. 5).

## Body surface area calculation

Body surface area is recommended as the principal basis for drug dosage[15 16] as the rate of metabolism or redistribution of a drug is proportional to metabolic rate, which in turn reflects heat losses which, as for any warm object, are generally proportional to surface area. Many measurements of organ size, fluid compartment volumes and assays of blood concentrations of drugs correlate well with BSA.[13 17–20]

While this is valid for most ages, some decrease below the BSA proportional dose is in fact appropriate when prescribing for children of less than approximately 18 months, typically 10 kg, as below that age there are differences other than size that should be borne in mind, that is: in the neonate, many enzyme systems are immature; neonatal renal clearance is approximately 50% of adults, reaching adult values at approximately 6 months; the half-life for many drugs is therefore longer in neonates and infants; and children have a higher total body water percentage than adults (80% at birth, 70% at 3 months and 60% at 1 year, compared with approximately 55% for adults). This is important when considering the distribution volumes of drugs; in children less than 1 yr of age, distribution volume is relatively large for drugs that are water soluble, and small for those that are fat soluble.[14 21–23]

Moore, in 1909,[19] was the first to recognize the importance of BSA, saying that: "stating dosage in reference to body weight is not only inaccurate, but rests entirely on a wrong principle", and that it should be:

> "proportionately instead to the body surfaces or, in other words, proportionately to the two thirds powers of their weights, which leads to quite different doses." (1)

Moore was using the same formula as Meeh,[24] who is widely quoted. Clark gave his name to his second rule by reporting Moore's work in 1937,[13] again recommending dosage proportional to the two-thirds power of body weight.

The history of actual measurements of surface area is fascinating, with examples of marvellous ingenuity, from covering surfaces with paper, plaster or lead, to "wrapping a human in silk tights, charging up the silk as one would a Leyden jar, and calculating the surface by applying a metal plate of known area".[25] The power of 2/3 is the ratio of surface area to volume of cubes, spheres and other such solid objects, and in humans appears to be a quite reasonable approximation (fig. 2) for those of normal build, using a proportionality constant of approximately 12 for kilograms, that is 12×wt$^{2/3}$.[25] It is, however, unidimensional.

The first multidimensional formula for surface area to be used widely was proposed by DuBois and DuBois:[26]

$$S=W^{0.425}\times H^{0.725}\times 71.84 \qquad (2)$$

where S=surface area (cm$^2$), W=weight (kg) and H=height (cm).

The nomograms derived from this equation are those seen most often, as for example in *Martindale's Pharmacopoea*[2] or *Geigy Scientific Tables*[27] despite the fact that the investigators only measured nine subjects.

The definitive work on surface area is a monograph by Edith Boyd[28] who improved the formula as follows:

$$S=3.207W0.7285–0.0188 \log W\ H0.3 \quad (3)$$

where W=weight (g). She quoted the SD in her subjects as 7%.

Gehan and George[29] summarized all existing data, and suggested a further marginal improvement on the above equations, namely:

$$S=0.0235H^{0\ 42246}W^{0.51456} \quad (4)$$

In fact, equations (1–4) are within 5% of each other to a value of 15 kg in subjects with a normal build. Thin subjects would appear to have approximately 10% more surface area than predicted by equation (1), and fat subjects approximately 20% less,[25] but unfortunately the literature does not provide reliable data on variations of BSA with build.

## BSA-based rules

The nomograms constructed from these formulae provide the actual surface area, from which further mathematics provide the fraction of an adult dose, and thence the required dose, but this is hardly a bedside calculation.

The consensus has generally been that fixed tables of percentages of an adult dose derived from BSA[3 20 30] are a lesser evil than calculations requiring such higher mathematical powers, although they do require interpolation and the consequent possibility of introducing further errors. This approach, first suggested by Butler and Richie[17] and popularized further by Catzel and Olver as "The percentage method"[31] is also difficult to use in a clinical situation: the values may be learned by heart, but this is little more use than nomograms or a calculator. They appear to be the basis of the table given in the *BNF*[1] (which does not quote its source) and many current textbooks: Catzel's values (table 1, fig. 3) follow the BSA curve up to 40 kg, from which point they are 5% higher. Differences in the percentages recommended in different sources appear to arise from a combination of approximations and differences in the size of an "adult" (whether 140 lb, 65 kg or 70 kg). Much of this work was done in the early part of the century, since when the normal adult has increased in size.

*Table 1* Catzel's Recommended Doses of Drugs for Children[31]

| Age | Weight (kg) | % Adult dose |
|---|---|---|
| 2/52 | 3.2 | 12.5 |
| 2/12 | 4.5 | 15 |
| 4/12 | 6.5 | 20 |
| 8/12 | 8.5 | 25 |
| 12/12 | 10 | 28 |
| 18/12 | 11 | 30 |
| 3 yr | 15 | 33 |
| 5 | 18 | 40 |
| 7 | 23 | 50 |
| 10 | 32 | 60 |
| 12 | 40 | 75 |
| 14 | 45 | 80 |
| 20 | 65 | 100 |

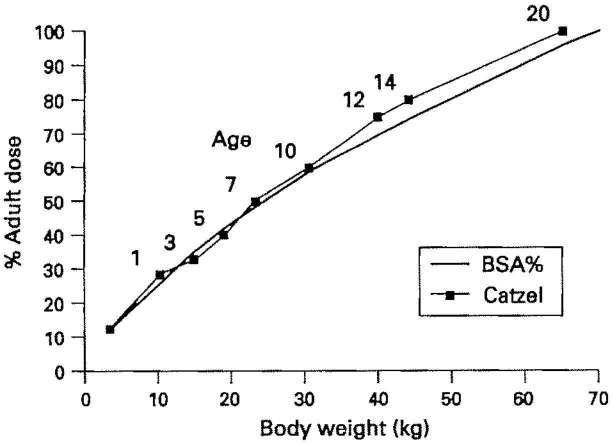

*Figure 3* Catzel's recommended doses of drugs for children as a percentage of adult doses.

## Salisbury rule

None of the rules described above is both simple and accurate enough for clinical use. A rule is needed that allows a dosage calculation that is approximately "correct", rather than having complicated mathematics in order to achieve academic accuracy, but getting the point wrong.

As a curve cannot be calculated easily with bedside mathematics, it was decided to use two straight lines crossing over at an appropriate point. As pointed out, the wt/70 (mg kg$^{-1}$) rule falls substantially below the BSA curve throughout its range, with consequent under dosing. Wt/50, which is the same as double the body weight as a percentage of the adult dose, makes for easier calculation and provides reasonable results up to 30 kg, although still deviating to the low side at low weights (thereby accommodating the reservations concerning infants described above). Over 30 kg, one may simply add 30 to the body weight to obtain the graph shown in figure 4, following the BSA curve closely.

The differences in the wt/70 (mg kg$^{-1}$) and Salisbury rules from the BSA curve are illustrated in figure 5.

Thus we propose the following rule in children:

less than 30 kg: weight×2
more than 30 kg: weight+30

percentage of the adult dose of a drug.

Expressed colloquially, this is: "to obtain the

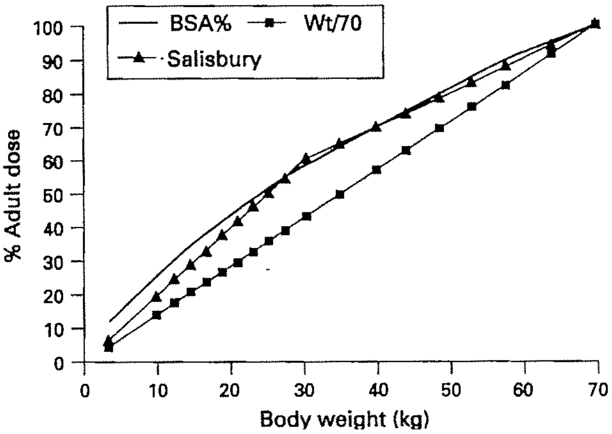

*Figure 4* The Salisbury rule for drug dosages for children compared with BSA and wt/70 (mg kg$^{-1}$).

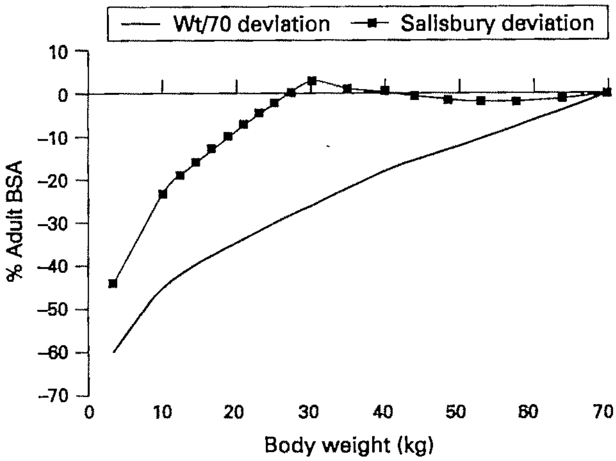

*Figure 5* Deviation from BSA of the wt/70 (mg $kg^{-1}$) and Salisbury rules.

*Table 2* Examples of drug dosage calculations using different rules. Most doses are rounded to the nearest milligram. n/r=Not recommended

| | Weight | | | |
|---|---|---|---|---|
| | 3.2 kg | 8.5 kg | 18 kg | 45 kg |
| Atracurium: "Adult" dose assumed to be 35 mg | | | | |
| 0.5 mg $kg^{-1}$ | n/r | 4 | 9 | 23 |
| Salisbury rule | n/r | 6 | 13 | 26 |
| Catzel/*BNF* | n/r | 9 | 14 | 28 |
| Thiopentone: "Adult" dose assumed to be 280 mg | | | | |
| 4 mg $kg^{-1}$ | 13 | 34 | 72 | 180 |
| Salisbury rule | 18 | 48 | 101 | 252 |
| Catzel/*BNF* | 35 | 70 | 112 | 224 |
| Morphine: "Adult" dose assumed to be 10 mg. "*BNF*" follows *BNF* guidance for different age/weight groupings | | | | |
| 0.1–0.2 mg $kg^{-1}$ | 0.3–0.6 | 0.9–1.7 | 1.8–3.6 | 4.5–9 |
| *BNF* mg $kg^{-1}$ | 0.5 | 1.7 | ~4 | 10 |
| Salisbury rule | 0.6 | 1.7 | 3.6 | 9 |
| Catzel | 1.25 | 2.5 | 5 | 8 |

BSA% from weight, under 30 double it, over 30, add 30".

Examples of this rule for some commonly used drugs are given in table 2. The results from the Salisbury rule fall into a safe area close to those recommended by the *BNF*. It is particularly useful that it removes the need to learn different doses at different ages. Therefore, for example, the dose for morphine is quoted in the *BNF* as: "<1 month, 150 μg $kg^{-1}$; 1–12 months 200 μg $kg^{-1}$; 1–5 yr 2.5–5 mg; 6–12 yr 5–10 mg". The Salisbury rule tracks these different doses accurately, so eliminating the need for different dosage recommendations at different ages.

We have been using this rule now for almost 10 yr. It has proved easy to use, and there has been no clinical evidence of inappropriate dosage.

## Summary

Nearly 90 yr ago the following suggestion was made: "For the great majority of drugs the method of stating dosage as so much per kilogram should be abandoned".[19]

It has often been repeated, and in order to provide a satisfactory alternative the Salisbury rule is that children should have:

"less than 30 kg, double the body weight; more than 30 kg, add 30 to the body weight"

percentage of the adult dose of a drug.

This rule gives as close adherence to fractional body surface area as is desirable, under dosing where immature development may be present, together with the added advantage of easier and more reliable calculation of the result.

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# Multimodal approach to control postoperative pathophysiology and rehabilitation

H. KEHLET

## Summary

Major surgery is still associated with undesirable sequelae such as pain, cardiopulmonary, infective and thromboembolic complications, cerebral dysfunction, nausea and gastrointestinal paralysis, fatigue and prolonged convalescence. The key pathogenic factor in postoperative morbidity, excluding failures of surgical and anaesthetic technique, is the surgical stress response with subsequent increased demands on organ function. These changes in organ function are thought to be mediated by trauma-induced endocrine metabolic changes and activation of several biological cascade systems (cytokines, complement, arachidonic acid metabolites, nitric oxide, free oxygen radicals, etc). To understand postoperative morbidity it is therefore necessary to understand the pathophysiological role of the various components of the surgical stress response and to determine if modification of such responses may improve surgical outcome. While no single technique or drug regimen has been shown to eliminate postoperative morbidity and mortality, multimodal interventions may lead to a major reduction in the undesirable sequelae of surgical injury with improved recovery and reduction in postoperative morbidity and overall costs. (*Br. J. Anaesth.* 1997; **78**: 606–617).

**Key words**
Surgery, stress response. Pain, postoperative. Complications, morbidity.

Despite continuous advances in anaesthesia, surgery and perioperative care, major surgical procedures are still beset with undesirable sequelae such as pain, cardiopulmonary, infective and thromboembolic complications, cerebral dysfunction, nausea and gastrointestinal paralysis, fatigue and prolonged convalescence. Clearly, such morbidity may be related to the level of anaesthetic and surgical skill, but complications may occur regardless of skill and no single technique or drug regimen has been shown to eliminate postoperative morbidity and mortality.

A common feature shared by all surgical patients is the widespread changes in organ function, the so-called surgical stress response.[1] These functional changes are believed to be mediated by the trauma-induced endocrine metabolic changes and activation of several biological cascade systems (cytokines, complement, arachidonic acid metabolises, nitric oxide, free oxygen radicals, etc). Although these responses have evolved presumably to confer an advantage for survival, they may, if amplified and prolonged, also contribute to erosion of body cell mass and physiological reserve capacity.

The key question in our understanding of the pathogenesis of postoperative morbidity is therefore related to the pathophysiological role of the various components of the surgical stress response and whether or not a modification of such responses may improve surgical outcome. More simply, one may ask why a technically successful operation, whether a colonic resection, hip replacement or cardiac operation, should result in an unsuccessful outcome. Additionally, if such surgical sequelae are controlled, one may ask if patients could undergo major surgery on an ambulatory or semi-ambulatory basis.

This article reviews current techniques for controlling postoperative dysfunction by reducing surgical stress and pain. It is hypothesized that multimodal interventions may lead to a major reduction in the undesirable sequelae of surgical injury with accelerated recovery and reduction in postoperative morbidity and overall costs. This discussion will focus on elective surgery, excluding trauma and multiple organ failure, which have been reviewed elsewhere.[2]

## Perioperative risk factors and pathophysiological responses to surgery

Several perioperative risk factors and neurohumoral responses to surgical injury may contribute to postoperative morbidity (table 1).

### PREOPERATIVE FACTORS

### *Pre-existing disease*

It is well established that concomitant disease and

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*Table 1* Perioperative risk factors or pathophysiological responses to surgery that must be recognized, avoided or treated in order to control perioperative physiology and reduce morbidity

| Factors | Effects on outcome | Treatment |
|---|---|---|
| Pre-operative | | |
| Concomitant diseases | Increase overall morbidity | Preop. assessment and optimization of organ function |
| Malnutrition | Increase infective complications, delays recovery | Preop. nutrition |
| Alcohol abuse | Increase overall morbidity | Preop. abstinence or perioperative alcohol administration |
| Intra-operative | | |
| Surgical stress | Increase organ demands, leads to catabolism, immunosuppression and organ dysfunction | Minimally invasive surgery, neural block, pain relief, pharmacological interventions |
| Blood transfusion | Increase infectious complications and risk of cancer recurrence | Avoid unnecessary use of blood |
| Heat loss | Increase surgical stress responses during rewarming phase | Reduce heat loss or use external heating |
| Post-operative | | |
| Pain | Impairs organ function and delays mobilization and overall recovery | Effective, dynamic pain relief with multimodal pain therapy |
| Immunosuppression | Increase infective complications and cancer recurrence | Stress reduction, immunomodulation, avoid blood transfusion |
| Nausea/ileus | Delays recovery and early oral nutrition, enhances catabolism | Pain relief using neural block and NSAID, reduce use of opioid, pharmacological intervention (serotonin antagonists, etc) |
| Hypoxaemia | Increase risk of cardiac, cerebral and wound complications (infection/healing) | Oxygen administration, mobilization, stress reduction, avoid sleep disturbances |
| Sleep disturbances | May increase postoperative hypoxaemia, fatigue and enhance stress | Stress reduction, pain relief, reduce use of opioid, reduce noise and night time interventions |
| Catabolism/muscle loss | Increase all-over morbidity and fatigue, delays recovery | Stress reduction, pain relief, active rehabilitation, early oral nutrition, electrical muscle stimulation, growth factors |
| Immobilization | Increase risk of thromboembolic and pulmonary complications, increase fatigue, hypoxaemia and loss of muscle | Pain relief, active rehabilitation |
| Drains/nasogastric tubes/traditions | Delays recovery, may increase infectious complications | Avoid unnecessary use, revise perioperative care programme |

organ dysfunction are strong determining factors of postoperative complication rates and duration of hospital stay.[3] Accordingly, several clinical guidelines and indices have been developed to assess cardiovascular,[4] pulmonary[5 6] and thromboembolic[7] risks. Such information may serve as a basis for quantifying perioperative risk and outline indications for prophylactic therapy. However, such predictive scoring systems do not *per se* reduce postoperative morbidity, and may be successful only when preoperative optimization of organ function reclassifies a high-risk patient into a more low-risk group.

### *Malnutrition*

Malnutrition is a well established perioperative risk factor, and several nutritional assessment scores have been defined.[8] However, pre- and postoperative nutritional support with parenteral nutrition has been shown to reduce morbidity only in high-risk, malnourished patients.[8]

### *Alcohol abuse*

Recently, preoperative alcohol abuse, even without overt alcohol-related organ dysfunction, has been described as an important operative risk factor.[9] The mechanisms include alcohol-induced immunosuppression, subclinical cardiac dysfunction and an amplified hormonal response to surgery.[9]

## INTRAOPERATIVE FACTORS

### *Surgical stress*

During and after surgical injury, the body responds with profound changes in neural, endocrine and metabolic systems in addition to alterations in organ functions.[1] These changes are characterized by increased secretion of catabolic hormones, decreased secretion or effects of anabolic hormones, hypermetabolism and increased cardiac work caused by autonomic system activation, impaired pulmonary function, pain, gastrointestinal side effects with nausea and ileus, a change in the coagulatory–fibrinolytic systems favouring coagulation and thrombosis, and loss of muscle tissue and immunosuppression.

Although the surgical stress response may represent a universally conserved cellular defence mechanism,[10] the stress-induced changes in postoperative organ function may also be implicated in the development of postoperative complications. Accordingly, the concept of "stress free anaesthesia and surgery" to attenuate the trauma-induced physiological responses with subsequent reduction of morbidity has been proposed.[11] In elective clean surgery the main release mechanism of the stress response is afferent neural stimuli from the surgical area.[12] In addition, several humoral substances such as cytokines, arachidonic acid cascade metabolites, nitric oxide, endotoxins and other biological cascade systems are involved.[1] The surgical stress response is related to the magnitude of surgical injury, and correspondingly lower morbidity rates are observed after minor surgical procedures, including minimally invasive surgery.

Based on the concept of "stress free anaesthesia and surgery" several strategies to reduce or prevent the surgical stress response have been developed[12 13] (fig. 1). A reduction in the degree of surgical trauma by minimally invasive surgery reduces protein catabolism and markers of inflammation (IL-6 and CRP), pulmonary dysfunction and convalescence, while early responses of catecholamines, cortisol and blood glucose are less modified.[14] The type of general anaesthesia for operation has no important effect on the stress response,[12 15 16] except for high-dose opioid anaesthesia which may inhibit intra-, but not postoperative catabolic hormonal responses.[15] Blocking the afferent neural stimulus by various neural block techniques with local anaesthetics is very effective in reducing the classical catabolic response to operation,[12 16 17] especially in lower body procedures and with the use of continuous extradural analgesia. Thus the usual increase in cortisol, catecholamines and glucose concentrations can be prevented, insulin resistance reduced, and glucose tolerance and nitrogen economy improved.[12 16 17] The unfavourable changes in the coagulatory–fibrinolytic systems are also modified in favour of less thrombosis formation, while most changes in immune function and markers of inflammation (acute phase proteins, IL-6) are unaltered by neural block and concomitant hormonal inhibition.[12 16 17] Pain relief by other techniques such as extradural or systemic opioids, NSAID or clonidine are less effective than neural block with local anaesthetics.[12 16]

Other strategies include administration of non-specific substrates[13] or specific fuels such as glutamine, arginine, omega-3 fatty acids, and growth factors and anabolic hormones, all of which may reduce catabolism.[13] Pharmacological reduction in the inflammatory response may include various cytokine (TNF, IL-1) antagonists, free oxygen radical scavengers and other agents inhibiting neutrophil activation and migration, but these measures have not yet been tested in elective surgery. So far, only glucocorticoids which counteract several proinflammatory substances (cytokines, complement, arachidonic acid cascade metabolites) have been studied in elective surgical procedures. These results suggest that a single large preoperative dose of methylprednisolone reduced pain, hyperthermia, IL-6 and PGE$_2$ responses, and improved conventional impairment in pulmonary function.[18] Obviously, any modulation in inflammatory response has to be weighed against potential side effects, including impaired wound healing and increased risk of infection. So far these questions have not been examined in large-scale studies.

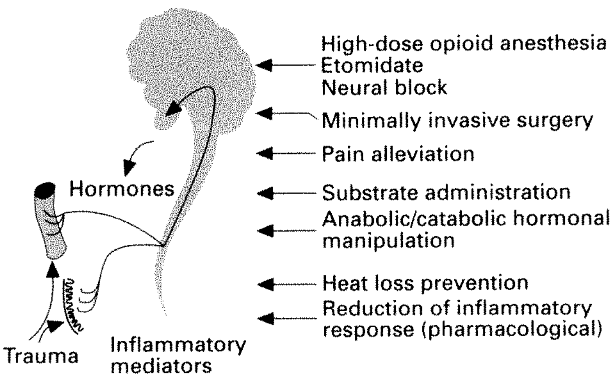
High-dose opioid anesthesia
Etomidate
Neural block
Minimally invasive surgery
Pain alleviation
Hormones
Substrate administration
Anabolic/catabolic hormonal manipulation
Heat loss prevention
Reduction of inflammatory response (pharmacological)
Trauma
Inflammatory mediators

*Figure 1* Interventions which may reduce the stress response to surgery.

In summary, although a reduction in surgical stress may be attractive based on neural block studies, further studies are needed to define those responses which should be suppressed and those which should be enhanced in order to improve outcome. Consequently, the most rational and effective anti-stress or anti-catabolic therapy has not been designed.

### *Heat loss*

Unintended intraoperative heat loss may be a significant risk factor leading to increased stress responses (cortisol, catecholamines, nitrogen loss) and cardiovascular complications.[19–21] Conservation of body heat and prevention of intraoperative hypothermia should therefore be provided whenever pronounced heat loss is expected, in order to reduce the stress responses to rewarming with increased oxygen consumption, catabolic hormone secretion and nitrogen loss.[19 22] This approach is supported by the finding that prevention of intraoperative hypothermia reduced wound infection rate and hospital stay in patients undergoing colonic surgery.[23]

### *Blood transfusion*

Increased blood loss and use of perioperative blood transfusion correlate with increased risk of infective complications and probably recurrence after cancer surgery.[24] The risk is related mainly to the content of white cells and non-cellular transfusion components.[24] Even the use of autologous blood transfusion with prolonged storage time may have detrimental effects, as toxic mediators (histamine, PAI-1, myeloperoxidase, etc) are released from leucocytes and platelets during storage for more than 2 weeks of any blood product containing these components.[24] Leucocyte-depleted blood by bedside filtration may significantly reduce postoperative infective complications.[25]

## POSTOPERATIVE FACTORS

### *Pain*

All surgical procedures are followed by pain, which may amplify endocrine metabolic responses, autonomic reflexes, nausea, ileus and muscle spasm, and thereby delay restoration of function. Optimal treatment of postoperative pain is mandatory in order to enhance recovery and reduce morbidity.

Presently, several techniques are available to treat postoperative pain effectively.[26] Initial therapy in minor to moderate sized procedures should involve a multimodal approach using incisional local anaesthetics, systemic NSAID and opioids.[26 27] With more severe pain, central neural block techniques using continuous extradural analgesia with local anaesthetics combined with small doses of opioids are necessary to provide dynamic pain relief, that is pain relief that allows normal function.[26 27] Patient-controlled analgesia techniques with opioids provide a high degree of patient satisfaction,[28] but pain relief during mobilization is less than that with the extradural combination techniques.[29]

The effect of improved pain relief *per se* on postoperative outcome is debatable.[12 16 17 26 28] Most controlled studies of extradural analgesia and patient-controlled analgesia have not demonstrated clinically important effects on outcome, except on some specific variables such as thromboembolism, gastrointestinal ileus and intraoperative blood loss (see below).[12 16 17 26 28] Surprisingly, effective pain relief does not automatically lead to increased ambulation and reduction in hospital stay.[30] Nevertheless, effective postoperative pain relief is a prerequisite to attain improved postoperative outcome, and when integrated into an active rehabilitation programme (see below) may reduce the surgical stress response, organ dysfunctions and improve gastrointestinal motility, to allow early oral nutrition and to facilitate early mobilization.

### *Immunosuppression*

Much evidence has emerged to demonstrate pronounced trauma-induced alterations in immunological systems. Major surgery causes immunosuppression with reduced delayed hypersensitivity response to recall antigen stimulation, T-cell-dependent antibody response, IL-2 production and HLA-DR antigen expression, IFN-$\gamma$ production and T-cell blastogenesis.[31] In contrast, neutrophil and macrophage functions are activated with increased release of oxygen radicals and TNF, and chemotaxis.[31] Smaller operations, including minimally invasive surgery, may result in less change in immune function.[14 31] Perioperative blood transfusion enhances postoperative immunosuppression.[24]

The clinical consequences of pre- and postoperative immunological changes are increased susceptibility to infective complications,[31–33] and probably increased risk of recurrence after cancer surgery.[31] Therefore, much effort has been expended to modify post-traumatic immune function, including the use of thymopentine, immunoglobulins, granulocyte colony-stimulating factor, glutamine, arginine and omega-3 fatty acids, PGG-glucan, histamine-2 receptor antagonists and other biological response modifiers.[31 33] Although most of these studies have shown partial improvement in post-traumatic immunosuppression and a tendency towards improvement in outcome, no final conclusions or clinical recommendations can be made. An exemption is the well documented relationship between the use of blood transfusion, immunosuppression and risk of infective complications.[24 25] Reduction in extent of trauma by minimally invasive surgery is presently the most effective technique to reduce immunosuppression and risk of infection.[14]

### *Nausea and ileus*

Nausea, vomiting and ileus are among the most common postoperative complaints and in addition to being unpleasant they may also be important determining factors in postoperative rehabilitation. Thus early enteral nutrition is critical in reducing post-traumatic infective complications[34] and may also reduce catabolism.[13] The pathogenesis of postoperative nausea, vomiting and ileus is multifactorial, being related to type of surgery, gender, choice of anaesthesia and use of opioids.[35 36] Efforts to reduce nausea and vomiting include the use of antiemetics, with serotonin antagonists being most effective, in addition to effective pain control and opioid sparing with the use of local anaesthetics, and NSAID.[35–37] Continuous extradural analgesia with local anaesthetics, but not opioids, is effective in reducing postoperative ileus[12 16 17 29] because the associated sympathetic intestinal nerve block increases motility. Such techniques should therefore be used whenever possible, in order to facilitate early oral nutrition and postoperative recovery.

### *Postoperative hypoxaemia*

Constant postoperative hypoxaemia lasts for 2–5 days after major abdominal surgery with superimposed episodic hypoxaemia occurring especially at night.[38] The mechanism of constant hypoxaemia is primarily a pulmonary shunt caused by reduction in functional residual capacity,[39] while postoperative episodic hypoxaemia may be caused by ventilatory arrhythmias (hypoventilation and apnoeas) related to rebound rapid eye movement (REM) sleep on the second and third nights after operation.[38 40]

Late postoperative hypoxaemia may be involved in cardiac, cerebral and wound complications. Thus postoperative myocardial ischaemia is a strong predictor of postoperative cardiac complications after non-cardiac operations[41 42] and some studies have shown a temporal relationship between the occurrence of episodic hypoxaemia and myocardial ischaemia and/or arrhythmias in the late postoperative period.[38] As episodic hypoxaemia is most pronounced at night and unexpected postoperative death seems to occur more often at night than during the day or evening,[43] further studies are urgently needed on the pathogenesis of hypoxaemia and its effect on cardiac morbidity. Late postoperative hypoxaemia may also be a factor in wound complications as reduced supply of oxygen to the surgical wound impairs healing[44] and lowers resistance against bacterial wound infection.[45] Finally, postoperative impairment in cognitive function and delirium may be related to postoperative hypoxaemia[46] and postoperative delirium has been treated successfully with supplementary oxygen.[47 48]

As late postoperative hypoxaemia may have important clinical implications for cardiac, cerebral and wound complications, the choice of analgesic technique may be important, as neural block techniques with local anaesthetics and avoidance or reduced use of opioids may improve oxygenation.[38] Also, early ambulation and avoidance of the supine position may improve postoperative oxygenation.[49] Although oxygen therapy may reduce postoperative tachycardia[50] and be of potential advantage for the wound[44 45] and brain,[46] no definite indications for dosage and duration of postoperative oxygen therapy have been determined. Nevertheless, based on the above mentioned considerations and duration of postoperative hypoxaemia, routine postoperative oxygen administration may be indicated for the first 2–4 days in high-risk surgical patients and in patients with an $Sp_{O_2}$ less than 93%. The use of late postoperative pulse oximetry monitoring is therefore recommended. In the early postoperative period in the post-anaesthetic care unit, pulse oximetry monitoring may indicate changes in care, although a reduction in all-over morbidity has not been documented.[51]

### *Postoperative sleep disturbances*

Sleep patterns are severely disturbed in postoperative patients, with a decrease in total sleep time, elimination of (REM) sleep and a marked reduction in slow wave sleep (SWS).[40 52] The pathogenesis of postoperative sleep disturbances is multifactorial, and includes afferent neural stimuli (surgical stress), cytokines, pain, use of opioids, and noise and awakenings during monitoring and nursing procedures.[52] Postoperative sleep disturbances with REM sleep rebound on the second to fourth night may be related to sleep-induced apnoeas, nocturnal hypoxaemia and profound sympathetic activation with haemodynamic instability.[40 52] Therefore, postoperative sleep disturbances may be a pathogenic factor in postoperative cardiac dysfunction and complications, in addition to mental dysfunction.[52] Prevention and treatment of postoperative sleep disturbances have not been evaluated, but may involve reduction in surgical stress, noise, inconvenient nursing procedures and provision of effective pain relief with reduced use of opioids.[52] Laparoscopic surgery may reduce postoperative sleep disturbance compared with open laparotomy.[53]

### *Immobilization*

Traditional perioperative care involves bed rest, although it is well known that immobilization may increase the risk of thromboembolic and pulmonary complications.[54] Furthermore, bed rest predisposes to orthostatic intolerance and instability during standing, and to an increased loss of muscle tissue and function.[54] Postoperative hypoxaemia is also more pronounced in the supine position[49] with its potential detrimental effects on cardiac, cerebral and wound function (see above). Finally, early ambulation may improve wound healing.[55 56] Despite this evidence, early ambulation has been controversial in the history of surgery,[57] although the movement towards ambulatory or semi-ambulatory surgery has supported the concept of early ambulation and rehabilitation in order to improve outcome and reduce costs. The prerequisite for early ambulation and active rehabilitation is effective dynamic pain relief using the multimodal approach (see above).

### *Catabolism and muscle wasting*

Postoperative catabolism and muscle wasting are important factors for development of postoperative fatigue[58] and in overall recovery. Catabolism is mediated by the surgical stress response, postoperative immobilization and semi-starvation. These physiological changes after routine major surgery may persist for up to several months in patients receiving established routine care.[59] Recovery of muscle strength is delayed further in old compared with young patients,[60] suggesting special efforts to be made in this high-risk group. Therapeutic interventions in order to reduce catabolism and loss of muscle tissue and function may include stress reduction (see above), enforced early mobilization, electrical muscle stimulation[61] and early oral nutrition,[8] supported by pain treatment techniques to accelerate restoration of gastrointestinal motility (see above). Furthermore, a variety of nutritional substrates, growth hormone or other growth factors may reduce catabolism and maintain muscle mass.[13 62]

### *Drains/nasogastric tubes/traditions*

Perioperative guidelines are usually developed according to traditional practice, which most often are not validated by scientific studies. These often include the use of drains and nasogastric tubes in addition to traditional "observation" periods in hospital. The traditional routine use of drains seems unnecessary based on available evidence from controlled clinical studies in several operations, including cholecystectomy,[63] joint replacement,[64] colonic surgery[65] and radical hysterectomy.[66] Enhancement of recovery and reduction of hospitalization may also be achieved by home discharge with a drain in place after mastectomy.[67 68] The routine use of nasogastric tubes after elective abdominal surgery is unnecessary and may even contribute to pulmonary complications.[69 70] Furthermore, routine use of nasogastric decompression may delay oral intake and thereby slow recovery because of other sequelae and semi-starvation (see above). Finally, traditional restrictions on early oral intake after abdominal surgery should be abandoned, as they are not supported by scientific data.[71]

These findings therefore suggest that increased efficiency and reduced costs can be achieved if traditional care programmes are adjusted to the available scientific data.

## Postoperative morbidity

Surgical procedures may be followed by undesirable sequelae such as cardiac, pulmonary, thromboembolic and infective complications, etc, which may not be related directly to imperfections in surgical or anaesthetic technique but rather to various perioperative risk factors and pathophysiological

*Table 2* Common postoperative complications, their pathogenesis and prevention

| Complication | Pathogenic factors | Interventions |
|---|---|---|
| Cardiac | Cardiac stimulation (surgical stress), hypoxaemia, fluid disturbances | Stress reduction (minimally invasive surgery, neural block, pain relief), oxygen administration, avoid heat loss and fluid overloading |
| Pulmonary | Impaired pulmonary and diaphragmatic function (surgical stress), pain, immobilization, fluid disturbances | Stress reduction (minimally invasive surgery, neural block, pain relief, physiotherapy, glucocorticoids), avoid supine position and fluid overloading |
| Thromboembolism | Altered coagulatory/fibrinolytic balance (surgical stress), immobilization | Antithrombotic prophylaxis, stress reduction (neural block, pain relief), mobilization |
| Cerebral dysfunction | Surgical stress, hypoxaemia, psychoaffective drugs, withdrawal syndromes | Stress reduction (minimally invasive surgery, neural block), oxygen administration, mobilization, avoid unnecessary opioid, psychoaffective drugs and development of drug withdrawal |
| Infection | Contamination, immunosuppression (surgical stress), hypoxaemia | Avoid contamination, use antibiotic prophylaxis, stress reduction (minimally invasive surgery, neural block), immunosupportive therapy, nutrition, oxygen administration, mobilization, remove catheters and drains as soon as possible, avoid unnecessary blood transfusion |
| Nausea and gastrointestinal dysfunction | Afferent stimulation (surgical stress), anaesthetics and opioid analgesics | Stress reduction (minimally invasive surgery, neural block, pain relief), avoid unnecessary opioids, use antiemetics |
| Impaired wound healing | Malnutrition, catabolism, (surgical stress), hypoxaemia, infection | Stress reduction (minimally invasive surgery), oxygen administration, mobilization, avoid infection, provide pre- and postoperative nutrition |
| Fatigue, reduced functional capacity and convalescence | Loss of muscle tissue and function, (surgical stress), immobilization and impaired cardiovascular adaptation to exercise, malnutrition | Stress reduction (minimally invasive surgery, neural block, pain relief), early oral nutrition and ambulation |

responses, including the effects of the surgical stress responses discussed above (table 2).

### CARDIAC COMPLICATIONS

Cardiac complications occur in 1–3% of patients undergoing major surgical procedures, with a higher incidence (2–15%) in those patients with preoperative cardiac risk factors.[42] Although improved intraoperative monitoring and cardiovascular support therapy have reduced cardiac morbidity during operation, most cardiac morbidity occurs from 1–4 days after operation, calling for more attention towards pathophysiological mechanisms of cardiac dysfunction during this period. The pathogenesis of postoperative cardiac morbidity is probably multifactorial, but increased sympathetic stimulation with tachycardia, cardiac hypermetabolism and increased work,[42] together with postoperative reduction in oxygen supply (hypoxaemia) may be most important. Reduction of post-surgical hypermetabolism and sympathetic drive may be achieved by pain treatment, where extradural local anaesthetic techniques are most effective and promising.[12,16,17] However, the evidence for a reduction in postoperative cardiac morbidity by extradural analgesic techniques remains inconclusive, possibly because optimal techniques have not been used and extended sufficiently into the postoperative period, and other risk factors, such as hypoxaemia or fluid overloading, have been neglected. Early postoperative systemic opioid analgesic treatment may reduce cardiac ischaemia,[72] but the overall clinical advantage has not been documented.

Future reduction in cardiac morbidity will probably involve stress reduction by effective pain alleviation techniques, together with therapeutic intervention against episodic and constant hypoxaemia, with a focus on the late postoperative period.

### PULMONARY COMPLICATIONS

Postoperative pulmonary complications (atelectasis, pneumonia) are assumed to be related to the obligatory postoperative impairment in pulmonary function.[39] In addition, intraoperative factors, including general anaesthesia and supine position, lead to impaired pulmonary function and atelectasis,[73,74] which may have further detrimental effects in the postoperative period. The pathogenesis of postoperative impairment of pulmonary function includes a pain-induced decrease in pulmonary mechanics and neurally reflex-mediated inhibition of diaphragmatic function.[5,39] In addition, various humoral cascade systems, arachidonic acid metabolites, cytokines, endothelial adhesion factors, etc, may contribute.[75] Finally, routine postoperative care involving the supine position for several hours daily may impair pulmonary mechanics and oxygenation.

So far, no technique is available to prevent postoperative impairment of pulmonary function and pulmonary complications. During operation a decrease in inspired oxygen concentration[76] and re-expansion of the lungs[77] may reduce or prevent the risk of atelectasis. The effect of chest physiotherapy (conventional or incentive spirometry) is debatable,[78,79] although a slight decrease in complication rate may be obtained.[79] However, these techniques have not been documented to be effective after postoperative pulmonary complications have developed.[79] Deep breathing exercises may be sufficient in low-risk patients and incentive spirometry reserved for high-risk patients.[80] Effective pain relief may improve, but not eliminate, postoperative pulmonary morbidity.[12,16,17] Changing position from the supine to the sitting or standing position is of obvious advantage[49,74] but requires effective pain relief to allow for sufficient ambulation. Also, pharmacological modification of some of the humoral cascade responses with preoperative glucocorticoid administration may have favourable effects on both pain and pulmonary functional impairment.[18] Finally, reduction in trauma by minimally invasive surgery improves postoperative pulmonary function and reduces pulmonary complications.[14]

Despite currently available therapeutic measures (intraoperative management, postoperative pain relief, pharmacological treatment, minimally invasive surgery, position changes and ambulation) postoperative pulmonary complications continue to be clinically important. However, intervention studies have mostly investigated unimodal therapy, but multimodal intervention may be more promising (see below).

## THROMBOEMBOLIC COMPLICATIONS

Postoperative thromboembolic complications continue to be an important determinant of outcome, despite the existence of several prophylactic regimens.[7] The pathogenesis of postoperative thromboembolism is the unfavourable change in all three components of Virchow's triad with a decrease in lower extremity blood flow, hypercoagulability and increased thrombocyte aggregation, impaired fibrinolysis and loss of vessel wall integrity. Amplifying factors are concomitant diseases and immobilization. Extradural analgesia with local anaesthetics may have favourable effects on all components of Virchow's triad.[12 16 17]

Several controlled studies have documented a pronounced reduction in thromboembolic complications (lower extremity thrombosis, vascular graft thrombosis and pulmonary embolism) after hip procedures, open prostatectomy, knee replacement and vascular surgery with the use of extradural anaesthesia and analgesia.[12 16 17] The effect of minimally invasive surgery on postoperative thromboembolic complications remains to be clarified. Although the reduction in trauma produced by laparoscopic procedures may reduce undesirable pathophysiological changes in coagulation and fibrinolysis, positioning in the reverse Trendelenburg position and pneumoperitoneum may have the opposite effects.[81] However, as early ambulation may be feasible after most minimal invasive procedures, these negative intraoperative factors may not be clinically important.

In summary, much evidence has accumulated that various single modality measures (antithrombotic regimens with heparins, systemic anticoagulation therapy, dextran, mechanical devices, extradural analgesia, ambulation) have resulted in a reduction in postoperative thromboembolism. Further reductions may be possible, and a multimodal approach, combining these techniques in accelerated programmes (see below) should be studied.

## CEREBRAL DYSFUNCTION

Delirium or other acute confusional states are common postoperative complications associated with higher mortality and complication rates, poor functional recovery and longer duration of hospital stay.[82 83] The incidence in major elective, non-cardiac operations in patients >50 yr may be approximately 5–10%.[82] Specific risk factors are age >70 yr, self-reported alcohol abuse, poor preoperative cognitive and functional status, and markedly abnormal preoperative serum electrolyte concentrations.[82] In addition, the use of psychoactive medications such as opioids (meperidine) and benzodiazepines may contribute to postoperative delirium.[84] Finally, postoperative hypoxaemia[38] and sleep disturbances[52] have been suggested to be risk factors for postoperative delirium. As several of these factors are involved in the surgical stress response, postoperative delirium may be improved by stress reduction using efficient neural block techniques. However, the data available from several controlled studies of such techniques have not demonstrated a reduction in postoperative delirium.[12 16 17 85] Unfortunately, in most of these studies single or short-term treatment was given, without taking advantage of the possibilities of early ambulation and restoration of pulmonary and muscle function. Provision of opioid-sparing analgesia with NSAID or local anaesthetics may be expected to reduce postoperative delirium, but more data are needed for a definitive conclusion.[37 86] Postoperative oxygen therapy has been effective against delirium in only a few small-sized studies.[47 48]

In summary, most studies have involved unimodal intervention strategies, and no major improvement in cerebral postoperative outcome has been documented from such studies. In contrast, multimodal intervention with oxygen therapy, early surgery and maintenance of cardiovascular stability in high-risk patients undergoing acute hip surgery showed a substantial reduction in postoperative acute confusional states and hospital stay.[87] In future, further improvement in cerebral outcome should be sought by multimodal intervention in accelerated stay programmes, including effective pain relief with enforced mobilization and nutrition (see below).

## INFECTIVE COMPLICATIONS

Despite rational and data-based guidelines for antibiotic prophylaxis, infective complications at the surgical site (the wound) or remote places (abscesses, sepsis, multiple organ failure) remain major postoperative morbidity problems. As host defence mechanisms are important to combat infection, efforts should be directed towards counteracting undesirable changes in pre- and postoperative immune function (see above). Such measures include reduction in blood loss and transfusion, enteral nutrition, immunomodulating drugs, use of minimally invasive surgical techniques and measures to avoid late postoperative hypoxaemia.

## GASTROINTESTINAL DYSFUNCTION

Postoperative gastrointestinal dysfunction includes motility disturbances resulting in nausea, vomiting and ileus, and other functional deficiencies which reduce the barrier against translocation of endotoxin and bacteria from the intestinal lumen.

Development of nausea, vomiting and ileus is dependent mainly on the site of injury, anaesthetic technique and use of opioids (see above). The mechanism of reduced postoperative stomach and colonic motility is predominantly neurogenic with activation of inhibitory sympathetic efferents.[12 16 17] The ileus reducing effect of continuous extradural local anaesthetic techniques is well documented.[12 16 17 29] Nausea and vomiting may also be a result of direct neurogenic stimulation of the vomiting centre, which may be counteracted by serotonin antagonists and reduced use of opioids.[35 36 88]

A systemic or gut insult may promote breakdown of gastrointestinal mucosal barrier function, leading to translocation.[89 90] Although experimental studies suggest that impaired mucosal barrier function and translocation may further increase the systemic stress response caused by absorption of endotoxin and other bacterial products, the prevalence of gut translocation and its relationship to infective and other complications remain to be established in surgical patients.[89 90] The role of fasting and route of feeding may influence the stress response to surgical injury or other injuries, as oral nutrition was found to reduce the response compared with parenteral nutrition in some[91] but not all[92] studies. Nevertheless, even short- term fasting for 1–2 days enhances catabolism.[93]

As controlled clinical studies have shown that early enteral nutrition is effective in reducing nitrogen loss,[13 94] postoperative infective complications and duration of hospital stay,[34 94] in addition to improving immune function,[95 96] every effort should be made for early institution of enteral nutrition. The relative importance of different components in the enteral nutrition regimens (standard diet *vs* enrichment with glutamine, arginine and omega-3 fatty acids) remains to be established.[13 95 96] Provision of early enteral nutrition requires a combined effort with omission of unnecessary nasogastric tubes, use of antiemetics and effective pain regimens to enhance gastrointestinal motility, again representing a multimodal effort in order to reduce postoperative organ dysfunction.

### IMPAIRED WOUND HEALING

In the postoperative patient several factors may contribute to impaired healing and susceptibility to infections. Such mechanisms include hypoxaemia[44 45] and the response to injury and sepsis.[97] Although the relationship between nutrition and wound healing remains to be clarified,[98] early enteral nutrition may enhance wound healing.[99] Furthermore, oxygen administration may reduce infection[45] and be expected to improve wound healing.[44] Therefore, efforts to improve oxygenation such as ambulation[49] or oxygen therapy are important. Early ambulation may also improve wound healing by other unknown mechanisms.[55 56] However, in some operations, for example mastectomy, prolonged immobilization may reduce formation of seromas.[100] Finally, the use of growth factors may have a future role in the postoperative management of wound dysfunction.[13]

In summary, effective therapeutic measures against impaired wound healing and infection may include a multimodal approach towards infective complications (see above), and aggressive pain treatment allowing early ambulation, prevention and treatment of hypoxaemia and early oral nutrition. However, although these views appear rational, there are no controlled data to support this concept.

### FATIGUE AND CONVALESCENCE

Postoperative fatigue is a common feature of the recovery phase and is related to the magnitude of surgical injury, postoperative impairment of nutritional status, loss of muscle mass and function, and postoperative impairment in cardiovascular adaptation to exercise.[58 101] Also, the preoperative level of fatigue may increase the risk of postoperative fatigue, while the level of preoperative anxiety is less important.[58 101] Reduction in trauma and stress by minimally invasive surgery reduces postoperative fatigue and preserves functional capacity.[102] Single modality treatment with effective pain control[58] or nutrition[58 99] have not significantly reduced postoperative fatigue. Most importantly, if nurses and physicians confine patients to bed in the postoperative period, the positive effects of effective pain treatment may not be obtained.[30] Therefore, a multimodal approach to avoid postoperative catabolism and loss of muscle tissue and function seems rational. Although no controlled data are available, such a combined approach seems to be effective in reducing postoperative fatigue and convalescence after colonic surgery.[103 104]

## Multimodal approach to control postoperative pathophysiology and rehabilitation—a unifying concept

The risks and morbidity associated with surgical procedures have been steadily decreasing in recent decades, primarily because of improvements in patient preparation for surgery, and anaesthetic and surgical techniques during operation. One of the most impressive changes has been the introduction of minimally invasive surgery. These developments have also contributed to increased use of ambulatory and semi-ambulatory settings for surgical procedures. Counteracting these beneficial developments is the fact that the proportion of elderly patients presenting for surgery is increasing, and that they represent a high-risk group with increased postoperative morbidity and mortality. Thus despite improvements, major surgical procedures may continue to be beset with well known "medical" complications, including myocardial infarction, delirium, pulmonary dysfunction, thromboembolism, infective complications, fatigue and prolonged convalescence.

Although there has been much effort to improve each of these specific outcome variables (i.e. preoperative assessment, antithrombotic and antimicrobial prophylaxis, etc), therapeutic strategies have usually focused on unimodal interventions. One explanation for the paucity of data with a more global view of the postoperative period probably lies with the traditional orientation of various specialty groups. Thus surgeons have usually focused on surgically oriented postoperative complications, such as wound infection, shock and anastomotic dehiscence, and have ignored those complications being more "medical" in origin, such as those within the cardiac, pulmonary and cerebral systems. Anaesthetists have focused on those problems arising in the intraoperative or immediate post-anaesthetic period with emphasis on cardiovascular and pulmonary function, but may not see the majority of such morbidity because it arises in the later postoperative period in the surgical ward. Additional progress in postoperative outcome may require more attention to the pathogenesis of common postoperative complications and more focused attention on the later postoperative period (1–4 days) where the peak incidence of complications occurs.

The key pathogenic factor in postoperative morbidity, excluding failures of surgical and anaesthetic techniques, is the surgical stress response with subsequent increased demands on organ function. Much knowledge of the mediators of this response has accumulated in recent years with emphasis on biochemical and endocrine changes,[1] and several techniques have been developed which may attenuate these potentially undesirable responses (fig. 1), thereby providing a sound basis to avoid unnecessary development of postoperative organ dysfunction and associated morbidity. The development of pain-alleviating regimens which allow early ambulation, techniques to reduce nausea, vomiting and ileus, realization that early enteral nutrition is important for recovery and reduction of infective complications, and the use of well established antithrombotic and antimicrobial regimens therefore represent the basis for a global approach to perioperative care. However, an important limiting factor for this approach is inherited from surgical traditions not founded on scientific data. Examples are the inappropriate use of drains, nasogastric tubes, limited oral intake regimens, restrictions on mobilization, observational regimens, etc. A key question to be asked on each postoperative day, for each surgical procedure, is therefore "Why is the patient in hospital today ?" in order to provide continuous analysis and solution to those factors limiting early recovery and contributing to postoperative morbidity.

A rational approach towards control of the postoperative period is therefore multimodal intervention, as shown in figure 2. Before operation, detailed information about the accelerated stay programme must be provided, possibly including a videotape programme. Such detailed preoperative information has been demonstrated in itself to result in less pain and reduction of postoperative stay decades ago.[105] Stress reduction may be provided by currently available techniques (see above and fig. 1), and sufficient pain relief by currently available multimodal regimens. Most importantly, pain relief has to be used for early aggressive ambulation and enforced enteral nutrition to avoid the conventional postoperative functional impairment. Finally, in some high-risk patients, the use of growth factors or other anabolic supportive agents may be indicated.[13]

Unfortunately, controlled clinical studies of such a multimodal intervention to support an accelerated stay programme are not available. However, several small lines of evidence suggest that such a multidisciplinary effort may result in pronounced improvement in surgical outcome and reductions in morbidity and hospital stay after mastectomy,[67 68] carotid endarterectomy,[106] hip replacement,[107 108] colonic resection[29 103 104 109 110] and coronary bypass.[111 112] In this context it is noteworthy that the combination of laparoscopic-assisted surgery, extradural local anaesthetic, early nutrition and ambulation, and avoidance of opioids reduced hospital stay to 2 days without fatigue or cardiopulmonary, thromboembolic or infective complications in 15 high-risk patients (median age 81 yr) undergoing colonic resection.[103 109] In addition, regionalization of major surgical procedures to one hospital to increase experience and accelerate recovery may reduce costs and improve outcome.[113]

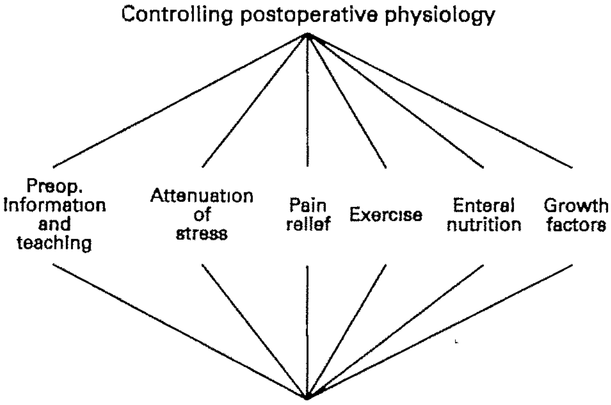
Controlling postoperative physiology
Preop. Information and teaching
Attenuation of stress
Pain relief
Exercise
Enteral nutrition
Growth factors
Reduced morbidity and accelerated convalescence

*Figure 2* Multimodal interventions towards control of the postoperative period

Multidisciplinary collaboration between patient, surgeon, anaesthetist, physiotherapist and surgical nurse represents an expansion of the more traditional "acute pain service" which merely serves to provide analgesia without taking part in the rehabilitation of the patient. We hypothesize that optimal results by postoperative "multimodal recovery intervention" may probably be best achieved by reorganization of the surgical wards into smaller postoperative "rehabilitation units" with a focus on early rehabilitation, nutrition and pain relief, and with a restrictive use of recovery-limiting procedures such as i.v. fluids, urinary bladder catheters, drains, tubes, etc. Such an approach may represent an important step to avoid the usual cascade to dependency in elderly hospitalized surgical patients, who are more sensitive to catabolic stress, immobilization, fluid changes and sensory deprivation.[60 114] Although accelerated stay programmes may reduce costs, these are not developed as enforced discharge programmes to save costs *per se*, but to take advantage of the improved postoperative functional status after such techniques, with early hospital discharge representing only an additional benefit.

## Future developments

Although major progress and improvements in surgical outcome may be expected by accelerated stay programmes, future research should be directed towards documenting such achievements from large-scale controlled studies or multi-institutional studies. In addition, the mechanisms of postoperative organ dysfunction within the first postoperative week should be explored further. In this context, further knowledge of the release mechanisms for the surgical stress response is required with information on the relative role of the different mediators which influence body organ functions. Presently, we have incomplete knowledge of which responses should be attenuated or stimulated, and which responses should be left unaltered. Nevertheless, the introduction of minimally invasive surgery, leading to reduction of catabolism, immunosuppression and other inflammatory responses with subsequent reduction of morbidity and convalescence, suggest that "stress-free anaesthesia and surgery" [11] may be valid. In this context, further developments in high technology surgery to reduce tissue injury will be promising. Furthermore, extension of research on biological modifiers[33] to improve postoperative immune function, on specific substrates such as glutamine and arginine to support gastrointestinal function and integrity and improve immunofunction,[13] and on various growth factors[13] are promising. Finally, it remains to be established if postoperative patients emerging from "stress free anaesthesia and surgery" with well-preserved organ function and who develop a later surgical complication because of a technical failure, are at reduced risk for subsequent development of multiorgan failure, sepsis, etc. This hypothesis deserves specific attention, as there is preliminary evidence that multiple physiological insults may be a mechanism for development of multi-system organ failure.[115] Thus development of multiple organ failure usually passes the phase of the more benign systemic inflammatory response syndrome (SIRS),[116,117] where the initial response to an elective operation may prime the body for development of detrimental consequences to a subsequent stimulus.

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# Concentration and second gas effects: can the accepted explanation be improved?

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**Summary**

During induction with high inspired concentrations of nitrous oxide, net uptake of gas produces a contraction in volume and a concentrating effect. In turn, this results in concentration and second gas effects. Most explanations of these effects are based on the common "rectangle" diagram devised by Stoelting and Eger and contain several inconsistencies which are explored here in order to produce a more accurate description. It is shown that in the standard diagram gas uptake is incomplete, there is ambiguity over functional residual capacity (FRC), equilibration with blood is inadequately represented and there is no representation of recirculation of anaesthetic. Compensation for loss of volume may be by means of an increased inspired ventilation, decreased expired ventilation or reduction in lung volume. Numerous accounts in the literature (including those based on the standard diagram) focus on the former mechanism at constant FRC. This has produced an unbalanced picture in which it is often implied that extra gas is routinely drawn into the lungs to replace that taken up. Significant compensation by this means cannot occur, for example when a constant volume ventilator is used. In discussing concentration and second gas effects, it is necessary to give a balanced view of the alternative mechanisms of compensation or to revert, as above, to a simple statement of the principle of conservation of volume. (*Br. J. Anaesth.* 1997; **78**: 618–625).

**Key words**
Anaesthetics volatile. Anaesthetics gases, nitrous oxide. Pharmacokinetics, uptake.Pharmacokinetics, nitrous oxide. Pharmacokinetics, lung.

In the early stages of anaesthesia with high inspired concentrations of nitrous oxide, large volumes of gas, of the order of 1 litre $\text{min}^{-1}$, are transferred from lungs to blood.[1] The disappearance of volumes of this magnitude manifests itself in various ways. As gas volume uptake commences, it is associated with one or more of the following: increase in inspired ventilation, decrease in expired ventilation or reduction in lung volume.[2] Simultaneously, "concentration" and "second gas" effects are detectable.[3–7] The precise relationship between these two types of phenomena remains confused in the literature and is often stated in terms that imply that the large volumes lost by uptake are always compensated for by large volumes of gas being drawn in automatically from the anaesthetic apparatus. In this article, the process of gas volume uptake is examined in a variety of circumstances, in some of which extra inflow provides only part or none of the compensation. In addition, most explanations of the concentration and second gas effects are based on the common "rectangle" diagram devised by Stoelting and Eger[7] and involve several anomalies—these are explored and a more comprehensive version of the diagram developed.

## Volume effects of gas uptake

In addition to being documented during anaesthesia with high inspired concentrations of nitrous oxide,[8] a reduction in functional residual capacity (FRC) occurs consistently in the anaesthetized patient under a wide range of unrelated conditions[9]: for example, during the use of halothane,[10] methoxyflurane[11] or isoflurane[12] in oxygen, or air–oxygen mixtures as the sole anaesthetic and during total i.v. anaesthesia (TIVA).[13] It is therefore reasonable to exclude a reduction in lung volume from the present discussion and limit our investigation to the effects of uptake on inspired and expired tidal volumes.

To simplify the discussion further, it is assumed that the patient is already anaesthetized by some other means, for example TIVA with 100% oxygen, the trachea intubated, connected to a non-rebreathing anaesthetic system and in a steady state at the time of introduction of nitrous oxide. Although differences exist between inspired and expired tidal volumes at steady state, owing to differences in the rates of exchange of oxygen and carbon dioxide, these are normally small and are also ignored, that is we assume a respiratory exchange ratio of 1.

Removal of gas volume by solution in lung tissue and blood may be reflected by a decrease in expired tidal volume or an increase in inspired tidal volume. Two extreme patterns are recognizable.[14–17] In one, the inspired tidal volume remains constant and equal

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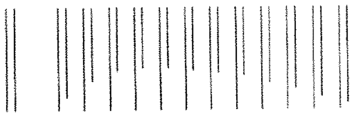
to its value during the control period. To compensate for the loss of gas volume, the expired tidal volume decreases. However, it does not remain the same from one breath to the next, reflecting the difference in uptake from breath to breath. Eventually, nitrous oxide uptake begins to decrease and expired tidal volume gradually returns towards its original level.

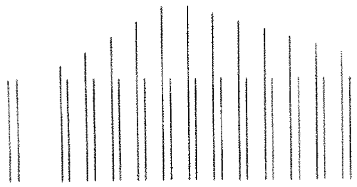
This sequence of events is illustrated in figure 1A, in which the first pair of vertical lines represents inspired and expired tidal volumes in the control period. Successive pairs of lines represent inspired and expired tidal volumes during later breaths at regular intervals thereafter, for example every minute.

At the other extreme, we have a pattern in which expired tidal volume remains constant and equal to its value during the control period. Inspired tidal volume must therefore increase to compensate for the gas volume lost during the breath. Again, it does not remain constant from breath to breath but increases to a maximum and then gradually returns towards its control value, reflecting the time course of nitrous oxide uptake. This sequence of events is illustrated in figure 1B.

We refer to these as "constant inflow" and "constant outflow" situations. The term "constant" is used here in the sense that in one case, the inflow is constant from breath to breath and equal to its control value, while in the other it is the outflow that is constant from breath to breath and equal to its control value.

It is probable that neither extreme pattern is attainable clinically but a constant inflow is approximated by using a ventilator which cycles from inspiration to expiration after a preset volume has been delivered, and behaves as an atmospheric pressure generator during expiration, that is a constant volume ventilator.[14 16 17] A constant outflow is approximated during the use of a ventilator which includes a feedback loop based on end-tidal $P\text{CO}_2$,[18] and during spontaneous ventilation[14 16 17] if end-tidal $P\text{CO}_2$ is maintained constant and equal to its value in the control period.


A Constant inflow


B Constant outflow

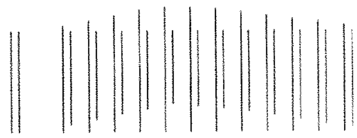

C Intermediate situation

*Figure 1* Schematic representation of different respiratory patterns seen during gas volume uptake with high concentrations of nitrous oxide: (A) constant inflow, (B) constant outflow, (C) intermediate situation. Each pair of vertical lines represents inspired and expired tidal volumes, respectively, for a particular breath. The left-most pair in each case represents inspired and expired tidal volumes for a breath during the control period. The remaining pairs represent later breaths at regular intervals (for example every minute) after introduction of a high inspired concentration of nitrous oxide.

If the subject is connected, in the control period, to a ventilator which cycles from inspiration to expiration at a preset pressure and acts as an atmospheric pressure generator during expiration, then inspired tidal volume increases to replace the gas volume lost by uptake during inspiration and expired tidal volume decreases to compensate for the continued loss of gas volume during expiration.[17] This situation is illustrated in figure 1C and is intermediate between the constant inflow and constant outflow extremes.

Nitrous oxide exchange, in common with that of other anaesthetic gases, involves an equilibration process between gas and blood.[19] At equilibrium, the concentration in blood = $\lambda$ times the concentration in gas,[19] where $\lambda$ = blood–gas partition coefficient. Thus, if $\lambda$ is constant, the process obeys Henry's law, that is the dissolved concentration is proportional to partial pressure.[19] This is usually the case with inspired partial pressures of anaesthetics used clinically. In general terms we would therefore expect that the greater the inspired concentration of nitrous oxide, the greater the uptake and therefore the greater the difference between inspired and expired tidal volumes at any time during washin. This should apply irrespective of whether or not we are dealing with a constant inflow, constant outflow or intermediate situation.

## Concentration and second gas effects

At the same time as the difference between inspired and expired tidal volumes finds expression in one or other pattern, it is possible to demonstrate that the higher the inspired concentration of nitrous oxide, the more rapidly the alveolar concentration approaches the inspired concentration.[3-5] This has been termed the "concentration effect". Any other gas administered simultaneously, for example 1% halothane, is also associated with a more rapid increase in alveolar concentration than would have been the case in the absence of nitrous oxide. This has been termed the "second gas effect".[6]

The standard diagram[7] used to discuss gas exchange in these circumstances is shown in figure 2. The figure consists of three rectangles which are described as representing events in a hypothetical lung. In the absence of a more detailed description, we interpret this to imply that the rectangles are a schematic representation of successive approximations to end-inspiratory alveolar gas volume, that is $\text{FRC}+(V_\text{T}-V_\text{D})$. The hypothetical lung is filled initially with 80% nitrous oxide, 19% oxygen and 1% second gas. Uptake of half the nitrous oxide (without simultaneous uptake of oxygen or second gas) produces the situation shown in the middle rectangle, with a nitrous oxide concentration of

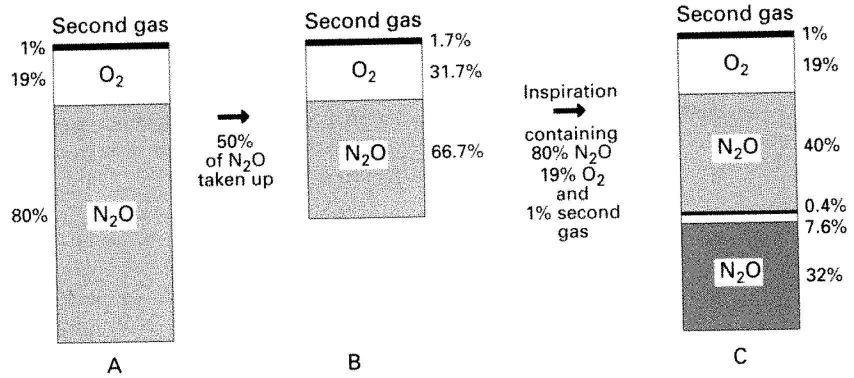


*Figure 2* Standard diagram of a hypothetical lung used to discuss gas exchange during nitrous oxide uptake. Percentages are of the total volume in each rectangle. Reproduced with permission from Stoelting and Eger.[7]

66.7%. To maintain lung volume, a further inflow of gas is necessary (B to C). This extra gas is shown having the same composition as in the first rectangle, and results in the concentration of nitrous oxide being increased further to 72%. The diagram or the associated explanation has appeared in numerous anaesthetic publications.[4 5 7 20–26]

Note that this treatment assumes that the second gas and oxygen are both insoluble (in the case of oxygen, a more realistic assumption[16] involves the exact replacement of oxygen uptake by carbon dioxide elimination, as assumed here).

Thus halving nitrous oxide initially present reduces its concentration from 80% to 72% instead of halving it to 40%. This argument has been used to explain the concentration effect by comparing this sequence with the situation where the initial nitrous oxide concentration is 1% and assuming again that half is taken up, but then replaced by almost pure oxygen,[5] so that nitrous oxide concentration is indeed almost exactly halved to 0.505%.

Meanwhile, the second gas which starts at a concentration of 1%, increases in concentration to 1.7% in the middle rectangle (a concentrating effect) and finally reaches 1.4% after being diluted by the increased inspiratory ventilation necessary to maintain lung volume (B to C). In figure 2, the solubility of the second gas has been assumed to be zero, and the increase in its concentration is seen to be caused by the concentrating effect. At the other extreme, if the second gas is very soluble, A to B takes the concentration from 1% towards zero, so that the concentrating effect associated with the uptake of nitrous oxide is much reduced. However, from B to C, the extra inflow restores the concentration of the second gas to at least 0.4%, so that the extra inflow seems to be more important.

Figure 2, as drawn, can also be interpreted as applying to a second gas which is soluble but with which the patient has been fully equilibrated before the carrier gas is changed from oxygen to a nitrous oxide–oxygen mixture. Thus there is little uptake of the second gas from A to B and its concentration is increased (although not quite to 1.7%) by the concentrating effect of the large uptake of nitrous oxide.

These comparisons have formed the basis of a hypothesis[7] that the further the second gas is from equilibration, the more its solubility determines which mechanism predominates—concentrating effect or extra inflow.

Note that the choice of the terms "concentration effect" and "concentrating effect" is rather unfortunate. The concentrating effect is an effect of uptake on concentration, whereas the concentration effect is an effect of concentration on uptake, that is on the rate of approach to equilibrium.

## Deficiencies in the standard gas-exchange diagram

It may be shown that there are four deficiencies in figure 2: (1) gas uptake is incomplete; (2) there is ambiguity over FRC; (3) equilibration with blood is inadequately represented; and (4) there is no representation of recirculation of anaesthetic.

These deficiencies are now considered in turn.

### INCOMPLETE UPTAKE

Although the gas present in the left-hand rectangle has been equilibrated in the sense that half the nitrous oxide has been removed, that in the extra inspired ventilation has not, a situation that is incompatible with the known behaviour of inert gas exchange.[19] This deficiency can be rectified by allowing half the nitrous oxide in the extra inspired ventilation to be taken up by blood. If we follow the reasoning used in the diagram, this results in a reduction in volume so that a further inspired ventilation is necessary and also has to be equilibrated. The process is depicted in figure 3, and continues for an infinite number of successively smaller steps to completion with a total uptake of nitrous oxide, and therefore a total extra inflow of inspired mixture, which is greater than that shown in figure 2, but still finite (267 ml instead of 160 ml).

The final concentrations of each agent may be deduced by inspecting each of the equilibrated portions, that is parts B, D, and F of figure 3 from which it can be seen that the final gas consists of an infinite number of portions each comprising 66.7% nitrous oxide, 31.7% oxygen and 1.7% second gas, so that this must also be the composition of the final gas mixture, that is the extra inflow is not associated with dilution and does not oppose the concentrating effect, as suggested previously. Note also that the representation of gas exchange as a stepwise process,

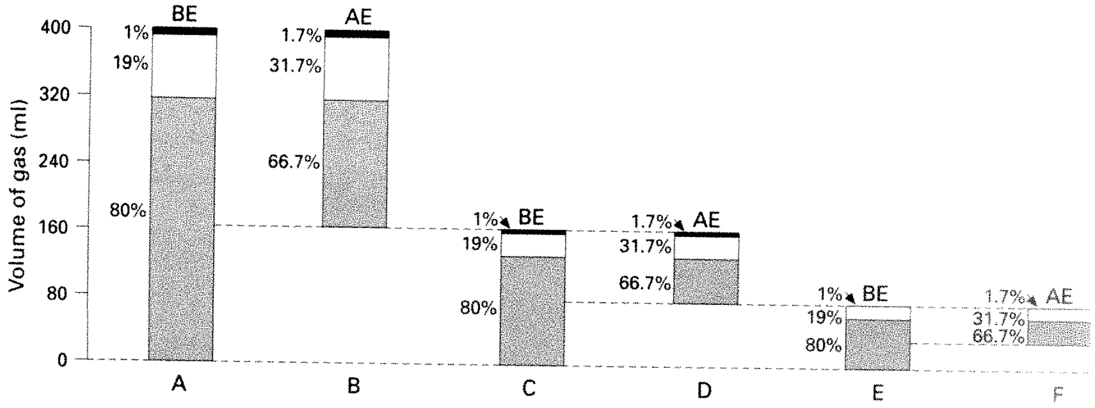


*Figure 3* Multi-step method of completing nitrous oxide uptake (stippling=nitrous oxide, white=oxygen, black=second gas). A: 400 ml of gas are contained initially in the "lung". B: The situation after half the nitrous oxide has been absorbed. C: Extra gas is brought in to replace the absorbed nitrous oxide. D: Half the nitrous oxide is absorbed from the extra gas. E: This necessitates a further inflow of gas from which half the nitrous oxide is removed (F). The process is continued until uptake is complete. The gas in the "lung" then consists only of equilibrated portions, that is B+D+F+... BE=Before equilibration; AE=after equilibration. Total uptake of nitrous oxide, and therefore the total extra inflow of inspired mixture, is finite (267 ml) but greater than in figure 2 (160 ml).

as shown in figures 2 and 3, is purely schematic; in reality, absorption and replacement occur concurrently.

## AMBIGUITY OF FRC

So far, figure 2 has been accepted as representing the events in the lungs as stated by the original authors.[7] This statement is now examined further.

The "lung" originally contains 80% nitrous oxide, 19% oxygen and 1% second gas. But this is also the composition of the inspired gas mixture (the "extra inspired ventilation" in the third rectangle). Such a situation applies only at the end of washin. However, when equilibration is complete, no further gas uptake occurs, contradicting the requirement that half the nitrous oxide be taken up.

An alternative interpretation is to regard the first rectangle in figure 2 as inspired tidal volume entering the lungs. The middle rectangle then represents what is left of this tidal volume after half the nitrous oxide has been taken up. There is, however, a problem with this interpretation, namely that when the inspired tidal volume enters the lungs and mixes with the gas in the FRC, the constituents of alveolar gas should appear in the expired tidal volume. For instance, if the subject had been breathing 100% oxygen during the control period, as assumed here, the concentration of oxygen in the expirate would be expected to be greater than shown in figure 2B.

This leaves us with a final interpretation of figure 2 in which the diagram is taken to represent an inspired tidal volume directly equilibrating with blood in the absence of FRC. Although this is an extraordinary assumption, it serves a useful purpose at this point in that it simplifies discussion of the volume effects of gas uptake and maximizes those effects by eliminating dilution of the inspired nitrous oxide in FRC.

Assuming zero FRC and uptake of half the nitrous oxide, we can now draw diagrams for the constant inflow and constant outflow situations. This has been done in figure 4. The first pair of rectangles represents the constant inflow case; these are identical to the first two rectangles in figure 2. An inspired tidal volume of 400 ml (fig. 4A), comprising 80% nitrous oxide, 19% oxygen and 1% second gas loses half of the nitrous oxide (160 ml) as a result of gas uptake and results in the expired tidal volume shown in figure 4B. The second pair of rectangles represents the constant outflow case. To maintain expired tidal volume constant and equal to 400 ml, the inspired volume has to be sufficiently in excess of 400 ml to provide for the uptake of half the nitrous oxide (267 ml) that takes place in going from figure 4C to figure 4D. Note that the total uptake in the second pair of rectangles is equal to the sum of the parts in figure 3.

## INADEQUATE EQUILIBRATION WITH BLOOD

In figure 4, the composition of the expired gas is the same, whether it is the inflow or outflow that is kept constant. This occurs because of the stated condition that "half the nitrous oxide be absorbed".[7] In reality, the fraction of nitrous oxide absorbed is not fixed but depends on equilibration between gas and blood, in accordance with Henry's law.[19] When this is allowed for, we obtain the situation shown in figure 5. Here we have assumed for convenience that each breath equilibrates with 400 ml of blood. $\lambda$ for nitrous oxide has, for simplicity, been assumed to equal 1 so that the concentrations of nitrous oxide must be the same in gas and blood at equilibrium. It has also been assumed that recirculation of anaesthetic has not yet occurred so that initially the blood contains no nitrous oxide. As before, the second gas and oxygen are assumed to be completely insoluble.

It can be seen that, after equilibration, constant inflow and constant outflow patterns are associated with different concentrations of each gas. In particular, in the constant outflow case, a larger volume of nitrous oxide enters the blood than in the constant inflow case (267 ml *vs* 221 ml), although this represents a smaller fraction (40% *vs* 55.3%) of an increased inspired volume (667 ml *vs* 400 ml). As a result, the concentration in blood is greater in the constant outflow case (66.7 ml% *vs* 55.3 ml%), that is equilibration is more advanced.

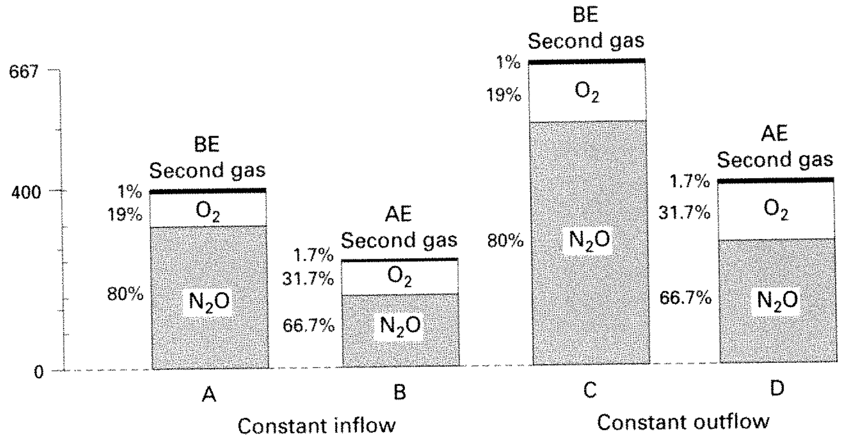


*Figure 4* Constant inflow and outflow cases before and after uptake. A–B: Inspired tidal volume is kept constant and equal to 400 ml. C–D: Expired tidal volume is kept constant and equal to 400 ml. BE=Before equilibration; AE=after equilibration. The gradations on each side of the *Y*-axis occur at intervals of 20% of the inspired tidal volume for each case, that is at intervals of 80 ml for the constant inflow case and 133.3 ml for the constant outflow case.

Each of the three gases in figure 5 has been subjected to a concentrating effect. To see this in relation to nitrous oxide it is helpful to distinguish, before equilibration, between nitrous oxide destined for absorption and that destined to remain unabsorbed. This has been done by using different densities of stippling. Thus the black areas in figures 5A and 5C represent nitrous oxide destined to be absorbed. The unabsorbed nitrous oxide is seen to increase its concentration from 24.7% to 55.3% in the constant inflow case and from 40% to 66.7% in the constant outflow case. The increase in concentration of each of the three gases is equal to the quotient of the initial and final gas volumes.

Concentration and second gas effects are both demonstrable in terms of figure 5. The second gas effect is obvious. Its cause, a concentrating effect associated with absorption of nitrous oxide, is also obvious. To demonstrate the concentration effect it is necessary to consider what would be different with a lower inspired concentration.

If the inspired gas had contained only 1% nitrous oxide (4 ml in the constant inflow case) then after equilibration with blood there would be 2 ml of nitrous oxide in 400 ml of blood (0.5 ml%) and 2 ml in 398 ml of gas (0.502%). Thus there would be negligible contraction of volume and a negligible concentrating effect. The result would be almost identical in the constant outflow case. In these circumstances, blood comes into equilibrium with only half the inspired concentration. On the other hand, at a high inspired concentration of nitrous oxide (80% in fig. 5), there is a marked contraction in volume, a marked concentrating effect and blood

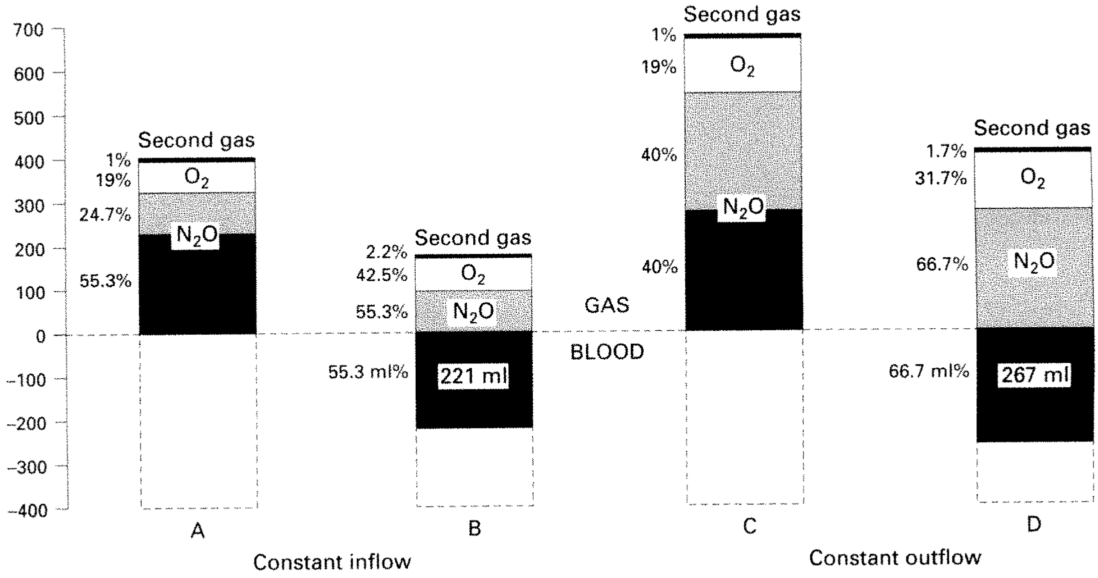


*Figure 5* Constant inflow and outflow cases before and after equilibration with blood. A–B: Inspired tidal volume is kept constant and equal to 400 ml. C–D: Expired tidal volume is kept constant and equal to 400 ml. The *X*-axis represents the gas–blood interface across which equilibration occurs. In A and C, the area outlined by the dashed line on the blood side of the gas–blood interface represents the 400 ml of blood, initially free of nitrous oxide, to be equilibrated with gas. For simplicity, λ has been set to 1. The black area=nitrous oxide destined for absorption, the stippled area=nitrous oxide destined to remain unabsorbed. The volumes of gas in A, B, C and D are 400, 179, 667 and 400 ml, respectively.

comes into equilibrium with much more than half the inspired concentration: (55.3/80)×100=69% for the constant inflow case and (66.7/80)×100=83% for the constant outflow case. Thus a high inspired concentration leads to uptake of a larger fraction of the inspired volume and hence to a more rapid approach to equilibrium, especially in the constant outflow case, but even when conditions are such that Henry's law leads to half the nitrous oxide being taken up (C to D in fig. 5), the final concentration is 66.7%, not 72%, as in figure 2.

### NO REPRESENTATION OF RECIRCULATION OF ANAESTHETIC

In figure 2, there is no representation of venous return and the associated recirculation of anaesthetic. Thus figures 2–5 each represents a "snapshot" of events before recirculation of anaesthetic. These deficiencies may be rectified and FRC incorporated simultaneously by reverting to a comprehensive computer model of anaesthetic uptake. When this is done, for example with the electrical analogue of Mapleson, it can been shown[16] that the constant outflow case is indeed always at a more advanced stage of equilibration during washin.

It is also possible to incorporate a non-zero FRC and recirculation of anaesthetic into the rectangle diagram. This has been done for the constant inflow case in figure 6 which is drawn for some arbitrary point during washin.

The diagram follows the same sequence as the mathematical model from which the existence of the concentration effect was first predicted,[3] that is instantaneous inspiration (fig. 6A) followed by complete mixing between the inspired tidal volume and the gas in FRC (fig. 6B), followed by equilibration with blood (fig. 6C), followed by separation into FRC and gas destined for instantaneous expiration (fig. 6D).

Using similar arguments to those used in relation to figure 5, it is possible to demonstrate the occurrence of concentration and second gas effects. Comparing figure 6 with the constant inflow case in figure 5, it can be shown that the reduction in gas volume for the breath decreases from 221 to 120 ml in absolute terms and from 55.3% to 5% as a percentage of the initial gas volume. This occurs because dilution of nitrous oxide in FRC and appearance of gas in the venous return both act to reduce the pressure gradient favouring nitrous oxide absorption. Accordingly, the concentrating effect is significantly reduced so that both concentration and second gas effects are reduced in magnitude, for example 35 ml% nitrous oxide in blood in figure 6 instead of 55.3ml% as in figure 5, and 0.614% second gas in the gas phase instead of 2.2%.

Of course, the values 0.5%, 30%, 69.5% in FRC and 5ml% in blood in figure 6A are all assumed. But whatever they are in practice at the beginning of a particular breath, a similar argument applies. The same is true if we use the constant outflow case and also if FRC is allowed to change in figure 6D instead of, or as well as, tidal volume. This last result should surprise no one as the principle of conservation of volume requires only that in the presence of net gas uptake, there must be a contraction in volume and a concentrating effect; maintaining lung volume is a convenient assumption in both the constant inflow and constant outflow models and is implied in the current treatment by the steady state condition with TIVA and 100% oxygen. Explanations of the concentration and second gas effects based on the relative solubilities of nitrous oxide and nitrogen merely restate the principle of conservation of volume in terms of the contributions of individual gases.

## A one-sided picture of gas exchange

An unfortunate consequence of the widespread use of

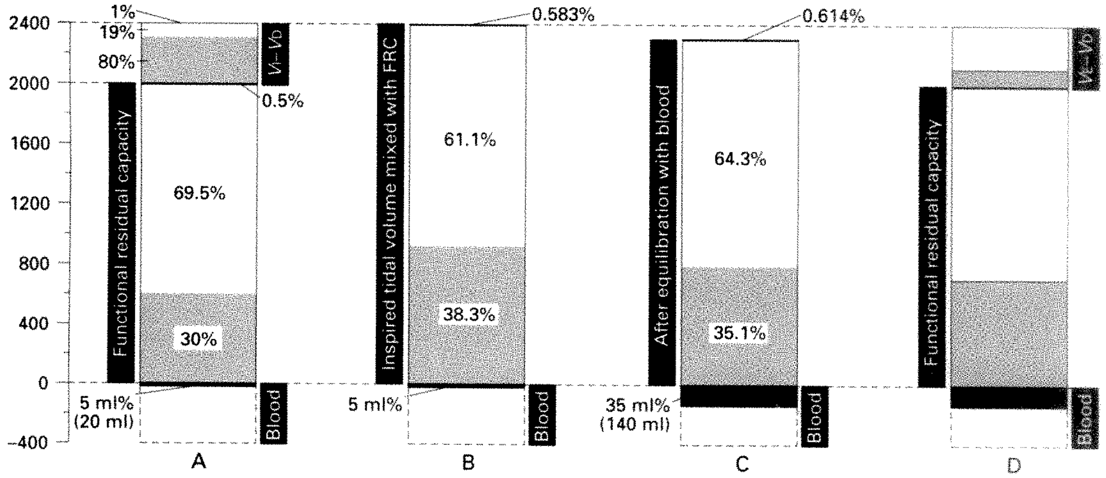


*Figure 6* Constant inflow case with FRC and recirculation of anaesthetic. Single respiratory cycle during washin of nitrous oxide. An inspired mixture of 1% second gas (black), 19% oxygen (white) and 80% nitrous oxide (light shading) is used with a non-rebreathing system. The *Y*-axis shows the volume of gas or blood (ml). A: From top down, 400 ml of inspired gas mixture ($V_I - V_D$); FRC 2 litre comprising 0.5% second gas, 69.5% oxygen and 30% nitrous oxide; 400 ml of blood for equilibration containing 20 ml of recirculated nitrous oxide (black area). B: After complete mixing of inspired gas with FRC. C: After equilibration of gas with 400 ml of blood ($\lambda = 1$ for nitrous oxide and 0 for oxygen and the second gas). Dissolved nitrous oxide is shown as black. D: From top down, expired alveolar tidal volume ($V_E - V_D$)=280 ml, FRC (still 2 litre) and blood, after equilibration.

figure 2 in texts on anaesthetic uptake is the implication that further gas is sucked routinely into the lungs during induction with high inspired concentrations of nitrous oxide. This concept has been expressed in various terms by different authors.[2,4,6,20,22–35] Although some accounts have not appealed to this phenomenon (e.g. Nunn[9]), or have used diagrams other than the standard diagram to help explain concentration and second gas effects (e.g. Hull[2]), the large number which have done so have conferred legitimacy on the underlying proposition.

There are three important aspects of these explanations with the emphasis varying from author to author: (i) gas is automatically drawn into the lungs to replace the volume loss caused by uptake, (ii) this is because otherwise lung volume would shrink, (iii) replacement is inevitable and beyond the control of the anaesthetist.

The problem with these descriptions is that they are limited in scope and fail to consider the alternative volume effects of gas uptake. Thus we can see from figure 1 that when authors write of an extra inspired ventilation[3,4,7,26] they are actually referring to the constant outflow case, in which an extra ventilation is readily identifiable. However, this requires not only constant lung volume but also constant expired ventilation, a point that is not usually stated explicitly.

Moreover, the implication that the anaesthetist has no control over the influx of this extra gas is demonstrably incorrect.[17] The anaesthetist decides whether or not respiration is to be spontaneous, and the type of ventilator to be used in the latter case. Ultimately, it is therefore the anaesthetist who decides whether there is an extra inspired ventilation, decreased expired ventilation or a combination of the two. Note also that in cases where a constant volume ventilator has been used,[7,29,31] extra inspired ventilation should never have come into consideration.

The preoccupation with the constant outflow case means that quantitative problems have often been cast solely in these terms to the exclusion of all other possibilities. The solutions obtained have not necessarily been universally applicable. For example, the concentration effect can be mimicked mathematically by a reduction in solubility.[16] One report of this property[36] was limited to the constant outflow case and overlooked an alternative mathematical expression that applies in the constant inflow case. Expressions for both cases were deducible in the original demonstration of this property.[16]

## Balancing the ledger

The merit of the standard diagram (fig. 2) is that it gives some indication of how the concentration and second gas effects arise, when previously they emerged only from the correct application of the principle of conservation of volume in a computer program[3,4] or in an electrical analogue.[16] As such the diagram has probably helped innumerable students to gain some insight into these effects.

The disadvantage of the standard diagram is that numerous anomalies appear when it is examined closely: implied assumption of zero FRC; omission of uptake from the additional inspired gas; absence of any consideration of the process of equilibration with blood, and hence of the influence of recirculation; and restriction to the case of constant FRC, constant outflow.

For teaching purposes, simple qualitative models are often ideal, as long as they do not materially mislead the student. Figure 2 implies that an extra inflow of gas must be associated with a diluting effect, a proposition that is challenged in figures 3 and 4. The extent to which it is worth introducing the successive corrections contained in our figures 3–6 is a matter of judgement, although we believe that they should be mentioned. In addition, it seems regrettable that most of the accounts of the concentration and second gas effects based on figure 2 deal only with the constant outflow case at constant FRC. Although two authors[2,21] make some passing reference to alternative circumstances such as the constant inflow case, their detailed account is solely of the constant outflow case, typical of spontaneous breathing, which tends to reinforce the impression of the inevitability of extra gas being "sucked in" to replace that taken up. Indeed, one of the present authors must plead guilty to this in one of his publications![37]

To the best of our knowledge, figures 3–6 have not appeared previously in the anaesthetic literature. We believe that they extend the understanding of the concentration and second gas effects. Figure 6 certainly mirrors the steps of Eger's mathematical model more accurately than figure 2 but a second diagram is then needed to demonstrate the constant outflow case. As a bare minimum, we believe that explanations should include the statement that the net uptake of gas produces a contraction in volume which inevitably leads to concentration and second gas effects, regardless of whether compensation for uptake is by extra inflow, reduced outflow, decreased lung volume or a combination of the three.

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*British Journal of Anaesthesia* 1997; **78:** 626–629

# CORRESPONDENCE

## Sternomental distance as predictor of difficult laryngoscopy

Sir,—I should like to comment on the article of Ramadhani and colleagues[1] which described the use of measurement of sternomental distance in the prediction of difficult laryngoscopy. The sensitivity and specificity of the test, using different "cut-off" or threshold values for sternomental distance, were calculated. The authors stated that "using discriminant analysis, a sternomental distance of 13.5 cm or less was calculated as the most accurate cut-off point for discriminating between difficult (grades III and IV) and easy (grades I and II) laryngoscopy". There is, however, no rigid statistical way in which cut-off values can be determined in diagnostic tests involving continuous quantitative data. Such values depend on the specific nature of the test and are usually determined by clinical consensus, based on whether or not an excess of false positives is less important than an excess of false negatives, or vice versa.[2]

In this study, the prevalence of difficult laryngoscopy was 0.035 (3.5%). This can be interpreted as the probability that a patient will present difficulty at laryngoscopy before the test is carried out, and so it is known as the prior probability. Similarly, the prior probability that the patient's trachea will be easy to intubate is 0.965. The positive and negative predictive values are the revised estimates of these probabilities in patients who are positive and negative to the test, and are known as the posterior probabilities The difference between prior and posterior probabilities at any given cut-off level is one way of assessing the usefulness of a test.[3] For the cut-off point of 13.5 cm, being test positive only increases the prior probability from 0.035 to a posterior probability of 0.076. In other words, being test positive only increases a patient's probability of being a difficult laryngoscopy by approximately 4 percentage points. Similarly, being test negative increases the prior probability of 0.965 to a posterior probability of 0.984, which represents an increase in probability of an easy laryngoscopy of only 1.9 percentage points.

More importantly however, before the fine details of optimum cut-off values are considered, it is imperative to evaluate the diagnostic accuracy of the test. Ramadhani and colleagues almost did this when they constructed a receiver operating characteristic (ROC) curve (a plot of sensitivity against (1−specificity) for each of a range of cut-off values), but they failed to calculate the area under this curve. It is the area under the ROC curve which determines the diagnostic accuracy. A "perfect" test is one whose ROC curve runs up the abscissa to a sensitivity value of 1, and then along a line parallel to the ordinate. The area under such a curve equals 1. A totally worthless test is one whose ROC curve runs along the line of identity. The area under such a curve equals 0.5.

I have calculated the area under the ROC curve of Ramadhani and colleagues to be approximately 0.71 (Simpson's method). What is also missing from Ramadhani and colleagues' data are the standard errors of the measured sensitivities and specificities. These are both binomial proportions taken from populations whose proportions are $p_{\text{sens}}$ and $p_{\text{spec}}$. The standard errors of these sample proportions are given by:

$$\text{standard error} = \sqrt{\frac{p\,(1-p)}{n}}$$

where $p$ can be estimated from the sample proportion (i.e. the sample specificity or sensitivity).[4]

Figure 1 shows the ROC curve re-drawn from the authors' data with the appropriate confidence intervals (+/− $t_{0.05}$ standard errors). These confidence intervals define the axes of the spindle shaped areas which contain the population data with 95% confidence. One such shape is shown for a sternomental distance of 13.5 cm. If the lowest points of these spindles are plotted, this creates the ROC curve seen in figure 2. This represents a "worst-case" ROC, but is within the 95% confidence limits of the data. The ROC curve in figure 2 follows closely the line of identity and the area under it is approximately 0.535. This implies that, from these data at least, measurement of sternomental distance as a predictor of difficult laryngoscopy may have a diagnostic accuracy approaching worthlessness.

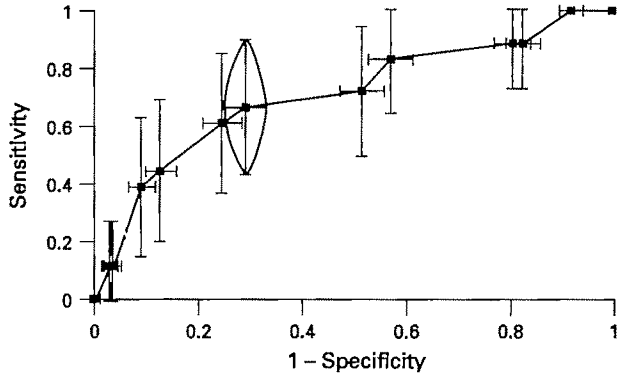

*Figure 1* Receiver operating characteristic (ROC) curve for sample data, with confidence intervals.

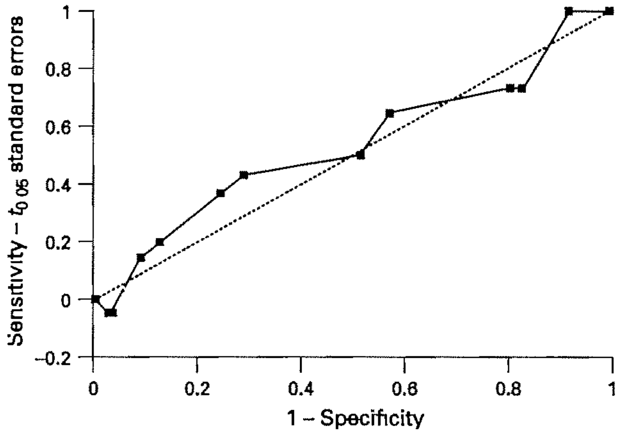

*Figure 2* Modified receiver operating characteristic (ROC) curve with data points from extremes of confidence intervals. Broken line=line of identity.

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Sir,—Thank you for the opportunity to reply to Dr Farmery's letter.

One of the statistical problems was to develop a rule, based on sternomental distance, that could be used to discriminate between easy and difficult laryngoscopy. One way of doing this statistically is by performing discriminant analysis. In our study, a linear discriminant function, $l=b\times\text{SMD}$ (sternomental distance) was calculated using parametric methods (i.e. using a measure of generalized squared distances, based on covariance matrices, but also taking into account the prior probabilities of the groups). In order to use $l$ for allocating patients to one of two groups, we had to specify a cut-off point, such that a patient can be assigned to one group if his score exceeds this cut-off value and to the other group if it does not.[1] It was shown that for a cut-off point of 13.5 cm the misclassification rate was minimized.

Although the ROC curve in this study was used mainly to illustrate the predictive properties of each of the cut-off levels, we agree with Dr Farmery that the area under the curve would have been useful for assessing the diagnostic accuracy.

Using the Trapezoidal method, we calculated the area under the ROC to be 0.71. The area under the "worst-case" ROC, as illustrated by Dr Farmery (i.e. plotting sensitivity $-t_{0.05}$ SE against $1-$specificity), was calculated to be 0.596. (Note that the appropriate way to estimate confidence intervals for proportions is by $p \pm N_{1-\alpha/s}$ SE, and not using the $t$ distribution as suggested by Farmery.[2]) Although this value is quite low, it should also be mentioned that the area for the "best-case" ROC (using sensitivity$+N_{1-\alpha/2}$ SE) was 0.828, which can be considered very good. Based on this interval, which clearly excludes an AUC of 0.5, we cannot, on statistical grounds, reject the measurement of sternomental distance as a worthless predictor of difficult laryngoscopy. In addition, we would again like to reiterate the message of our article which was that sternomental distance could not be used on its own as a sole predictor of difficult laryngoscopy but should be added to a series of simple preoperative tests.

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## Neuromuscular block in children

Sir,—In her editorial, Dr Hunter states that anaesthetists should question if they are using too much neostigmine and suggests that a reduced dose of 1.25 mg may be preferable in adults.[1] However, there is no mention of the incidence of postoperative residual curarization (PORC). While this is rare in children,[2] PORC occurs in up to 48% of patients with agents such as pancuronium and curare.[3,4] With the introduction of atracurium and vecuronium, the incidence of PORC is reduced, but is still a significant problem. Myself and my colleagues recently demonstrated that PORC affects 12% of adult patients after a bolus of one of these two drugs and occurs in 24% after infusions.[5] Moreover, we demonstrated that even those patients in whom a peripheral nerve stimulator was used during operation did not have a reduced incidence of PORC. Other workers have also shown PORC to occur in 9% of patients who had received vecuronium.[6]

Given the premise that PORC still occurs commonly even with intermediate acting non-depolarizing agents, I question the rationale and evidence for reducing the dose of neostigmine in adults. PORC may result in hypoventilation and inability to protect the airway, in addition to being subjectively unpleasant for conscious patients. Moreover, because side effects of neostigmine are relatively minor compared with the potential serious adverse sequelae of PORC, I would urge caution in reducing the standard dose of neostigmine until the safety of this has been confirmed.

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Sir,—Thank you for the opportunity to reply to Dr Fawcett's letter. As I expressed in my editorial,[1] the need for caution when deciding not to use an anticholinesterase to antagonize residual neuromuscular block is paramount. This is particularly so if aminosteroids are used: I believe one should not consider omitting the anticholinesterase after these drugs. The increased incidence of residual curarization after the use of the longer acting agents, pancuronium and tubocurarine, is one reason to select atracurium or vecuronium, even for long surgical procedures.

When using the benzylisoquinoliniums, I stressed the necessity to monitor neuromuscular block throughout anaesthesia if an anticholinesterase is to be omitted. The weakness of Dr Fawcett's argument is that in his retrospective study,[2] some of the patients were monitored for the first time in the recovery room. Even in the patients who were monitored peroperatively, the clinical practice of the anaesthetist, as much as the neuromuscular blocking drug, could be at fault in preventing full recovery from neuromuscular block before extubation. For instance, if the anticholinesterase is given before recovery from block is established, or if time is not allowed for the anticholinesterase to act, recovery may be inadequate on arrival in the recovery room. Obviously, there is a need for a large prospective study of PORC in patients who have been given varying doses of anticholinesterase at different degrees of recovery from block induced by varying neuromuscular blocking drugs. But the use of smaller doses of neostigmine has been demonstrated repeatedly to produce good recovery after atracurium and vecuronium, provided the anticholinesterase is not administered until 20% recovery of the first twitch of the train-of-four response. The time to full recovery after administration of neostigmine is longer than many anaesthetists realize, at least 7–10 min.[3,4]

I suspect we would agree that continuous neuromuscular monitoring is essential throughout anaesthesia and until tracheal extubation, whether or not an anticholinesterase is used. When an anticholinesterase is given, it should not be administered until recovery is well established (at least two twitches of the train-of-four response are present) for full recovery from block to be reliably obtained. This is particularly pertinent when repeated bolus doses or a continuous infusion of a neuromuscular blocking agent is used.

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## Cutting paediatric tracheal tubes—a potential cause of morbidity

Sir,—We wish to describe a critical incident that occurred at our institution recently. A child of 13 months required prompt tracheal intubation and ventilation as part of the management of acute meningitis. After induction of anaesthesia the trachea was intubated easily with a size 3.5 mm internal diameter tracheal tube, a single use Blue Line tracheal tube (SIMS Portex Ltd

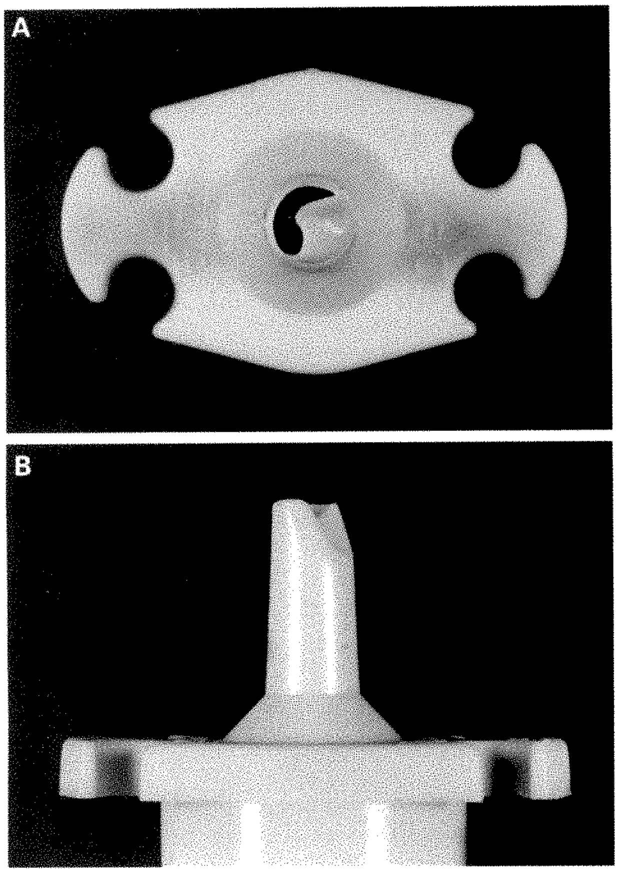

*Figure 1* End and side views of the Portex connector showing partial occlusion.

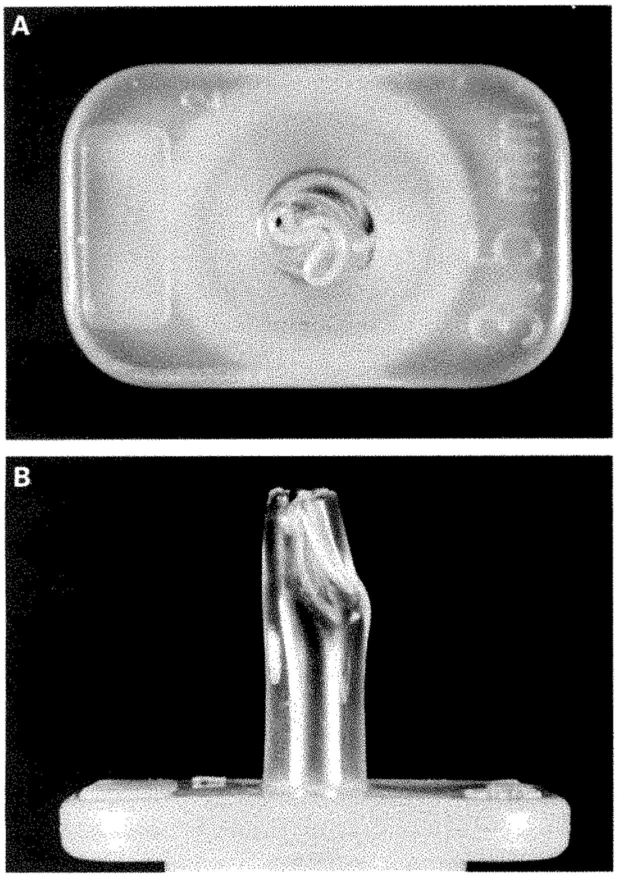

*Figure 2* End and side views of the Mallinckrodt connector showing complete occlusion.

Hythe, England) which had been cut to 14 cm immediately before use. Although the child's lungs could be ventilated, a 4-French gauge endobronchial suction catheter could not be passed through the tube to aspirate pulmonary secretions. The tube was therefore changed. A Contour tracheal tube (Mallinckrodt Medical UK Ltd) of the same size, also cut immediately before use, was inserted in its place. On this occasion we were unable to ventilate the child's lungs. It rapidly became apparent that this tube was completely occluded and it too was changed. This occurred uneventfully.

On subsequent detailed inspection it was discovered that both tubes had suffered the same complication (see figs 1, 2). The plastic 15-mm connector, while being inserted into the cut tube by an experienced operating department assistant (ODA), had buckled inwards occluding its distal lumen. This occlusion was very difficult to see from routine external inspection of either tube, which is why the problem was not detected when the equipment was checked rapidly before use by the anaesthetist and the ODA.

Portex Ltd and Mallinckrodt Medical are unaware of any previous description of this problem occurring in standard sized connectors and are investigating the respective tubes for manufacturing defects. A similar problem has been described only in 8.5-mm Minilink connectors for 3.0-mm and 4.0-mm Portex Blue Line tracheal tubes[1] when the problem was blamed on excessive twisting during re-insertion of the connector.

In this case the clinical urgency of the situation resulted in the tubes being checked less thoroughly than normal, and probably also accounted for any excessive force that may have been used in re-inserting the connectors. It is therefore important to recognize that the situation could have been avoided entirely by using an un-cut tracheal tube. While texts on the management of paediatric emergencies still provide formulae for calculating the length to which tracheal tubes should be cut,[2] we feel that in the emergency situation the practice of cutting tracheal tubes immediately before use should be discouraged. It not only takes longer but, as this incident demonstrates, is also a potential source of disaster.

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## Lead by example

Sir,—I was recently unfortunate enough to require a general anaesthetic myself. I was admitted to a teaching hospital with a prolapsed intervertebral disc and was to undergo a microdiscectomy. As the second patient on the list, I was seen 30 min before going to theatre, by a first-year specialist registrar, who was in the first week of his neurosurgery attachment. He was uncertain of his supervising consultant's proposed postoperative analgesia plans and was clearly intimidated in talking to another anaesthetist.

The consultant was still transferring the previous patient to recovery when I arrived in theatre and had asked the trainee to proceed. A dose of fentanyl was followed rapidly by thiopentone and a neuromuscular blocking agent, and the next thing I remember was a gagging sensation as the tracheal tube snagged on my arytenoid cartilages before entering the trachea. The combination of sensory input and no motor response was difficult to describe, but it was certainly unpleasant, and I am sure that for someone without any anaesthetic knowledge, would have been terrifying.

Despite mentioning this occurrence to the ward nurses after operation, I did not see an anaesthetist again before my discharge 2 days later. This experience has highlighted one or two areas of training that I feel need to be addressed.

Where trainees are with a consultant for a teaching list, it is not unreasonable for the trainee to be asked to see the patients for the remainder of the list, when the first patient is on the operating table. In many specialties, it is not possible to publish a list the day before, as a major part of the workload may be emergencies. However, if a trainee is sent to see patients, it is vital that they know what the consultant is proposing to do, and how it is to be undertaken. Consent for anaesthetic must be as informed as consent for surgery. Detailed explanations of the anaesthetic procedures and their associated risks must be provided. If the consultant does not provide sufficient information, the trainee should seek further clarification before seeing the patient. If trainees do not feel confident that they can explain the procedure adequately to the patient or are not aware of the potential complications of the procedure to be undertaken, they should request a joint visit with the consultant to see how the explanation should be given. In these litigious days, uninformed consent can be the basis for many legal actions. Very few trainees ever see consultants inform their patients about anaesthetic procedures, risks or complications, and this is an area which could be improved.

My second point concerns the practice of postoperative visits by anaesthetists As a trainee, I was taught that the list had not finished until patients had been reviewed on the ward after their operations Sadly, postoperative visits to NHS patients are becoming less common. A recent survey in Bath revealed that only 14% of NHS patients were seen on the ward after operation by an anaesthetist, even though the proportion approached 90% in the private sector. The main reason cited for this was that sessions funded for postoperative visiting in the NHS were being taken up by other clinical and administrative duties, whereas in the private cases, a postoperative visit resulted in an additional payment.

Trainees pick up the habits of their trainers. If they see cosultants neglecting their responsibilities, and not visiting patients after the list has finished, or the following day, it is not surprising that postoperative visits are becoming a thing of the past, with very little perceived value to managers. If the present trend continues, will preoperative visits be the next victim?

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# CHANGE IN EDITORIAL ARRANGEMENTS

From June 1, 1997, all new manuscripts and correspondence to the Editor of the *British Journal of Anaesthesia* should be addressed to:

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*British Journal of Anaesthesia* 1997; 78: 630–631

# BOOK REVIEWS

*Fiberoptic Endoscopy and the Difficult Airway*, 2nd Edn. A. OVASSAPIAN. Published by Lippincott-Raven, New York. Pp. 279; indexed; illustrated. Price £103.50.

This book is the second edition of a successful monograph published in 1990 as *Fiberoptic Airway Endoscopy in Anesthesia and Critical Care*. This new edition covers not only fibreoptic tracheal intubation, but also several situations where skilled management of the airway is required. The author points out in the preface that the airway is related to major morbidity and mortality of patients more frequently than is believed and stresses the importance of knowledge and mastering of the skill of airway management. To reflect this view, this edition has been expanded, carefully revised and updated. Five new chapters, including important factors such as safe methods of sedation and the methods for extubating difficult airways, have been added.

In the first of 15 chapters, specifications and functions of the fibreoptic endoscope are described. Sections for cleaning and sterilization are useful: several "do's" and "don'ts" are provided for the use and care of the device. The next two chapters deal with anatomy and pathology of the airway. Several colour photographs of fibreoptic views and more than 40 radiographic images, which are nicely labelled, cover the most relevant pathology. The latter chapter is outstanding.

In chapters four and five, methods of applying topical anaesthesia to the airway and of sedation of patients during fibreoptic procedures are described: in the former, pharmacological features of local anaesthetics, techniques of applications, complications and prevention of complications are discussed. An important concept of the technique—"conscious sedation"—is proposed. In this section, the importance is stressed of providing sedation, analgesia and amnesia, while maintaining communication with the patient, a patent airway and adequate ventilation. Methods to achieve such a state are described succinctly. This is followed by guidelines for non-anaesthetists who might use this technique.

In the subsequent three chapters, techniques are described for fibreoptic tracheal intubation in adults and children and for fibreoptic bronchial intubation. Several drawings and corresponding fibreoptic views allow clear understanding of each procedure.

In chapter nine, several uses of the fibreoptic endoscope in the intensive care unit are shown: evaluation and management of the compromised airway, confirmation of the position of the tracheal tube and exchange of tracheal tubes. Again, drawings and photographs are provided.

The next five chapters focus on difficult airways. The causes, prediction and management of difficult airways are described in a logical sequence. The usefulness of the laryngeal mask and oesophageal airway devices in difficult airway management is highlighted. The book ends with a step-by-step learning method of fibreoptic procedures.

Overall, Professor Ovassapian has achieved his intended goal with great success. This second edition should be useful to specialists of any discipline who engage in airway management. However, non-anaesthetists might find this textbook more useful if the sections for the effects of fibrescopy on haemodynamics or respiratory functions and those for the proper monitoring and management of the patient during the procedure were more comprehensive.

One major difficulty associated with the use of the fibreoptic endoscope is how to learn or teach it. The abundance of clear drawings and photographs in this textbook should enable tutors to teach trainees with considerable ease. We are sure that any person who uses the fibreoptic endoscope will find this book indispensable. Books of this type should be used frequently, rather than just read at libraries, to teach or to acquire the skill. This book is slim enough (279 pages) to carry around and the high quality paper will tolerate extensive use. Every library should ensure that a copy is readily available. All in all, an excellent book.

*T. Asai*
*R. S. Vaughan*

*Textbook of Anaesthesia*, 3rd Edn. A. R. AIKENHEAD AND G. SMITH (editors). Published by Churchill Livingstone, Edinburgh. Pp. 788; indexed; illustrated. Price £40.00.

What did you read over Christmas? I had the pleasure of browsing through the latest edition of Aitkenhead and Smith. The first edition of this book was published in 1985 and the production of the third edition in 1996 testifies to its popularity. In the past decade Aitkenhead and Smith has become the first choice of many new trainees in anaesthesia. The editors have recruited a considerable number of new authors to ensure a thorough revision of previous contributions. All of the authors have served the editors well, as most chapters are readable, comprehensive and up to date. It is notable that the editors have a major, personal commitment to this book in the form of authorship of nine of the 43 chapters. The majority of authors are associated with the departments in Leicester and Nottingham or perhaps reflect the time spent by the editors working in Scotland. Nevertheless, there are contributions from other anaesthetists; for example Wildsmith, Reilly, Hunter, Fee, Simpson, Willatts and Zideman are well known, authoritative authors

It is easy to find minor aspects of the book to criticize, but deciding on the balance of contents in a book for new trainees must be very difficult. I have doubts about the value of a chapter on the intensive care unit or a short chapter on the management of chronic pain. Some of the topics included in a single chapter do not lie well together. Gynaecological, genitourinary and orthopaedic surgery are strange bed-fellows, but plastic, endocrine and vascular surgery are probably not even on speaking terms.

These quibbles do not detract from an excellent book. Tight editorial control has ensured a coherent style and there is a profusion of figures and tables, a useful list of appendices and a good index. The text is not referenced but a short list of further reading is given at the end of each chapter. The usefulness of this list varies greatly. At a cost of £40 the book represents superb value for money. The reproduction of some figures is less than clear and the binding is unlikely to cope with hard use. However, when the book finally disintegrates, I will happily pay another £40 to replace it.

Both editors have been associated with several other books. I believe that this is their most successful venture; they identified a need and have met that need precisely. The price of this success is that they will soon have to think about the fourth edition.

*G. M. Hall*

*Smith's Anesthesia for Infants and Children*, 6th Edn. E. K. MOTOYAMA AND P. J. DAVIS (editors). Published by Mosby, Chicago. Pp. 999; indexed; illustrated. Price £99.00.

This is the 6th edition of Robert Smith's textbook, first published in 1959. It has long been an established and authoritative multi-authored work. The list of contributors reads as a "who's who" of paediatric anaesthesia in North America.

The growth of knowledge in this area is reflected in the size of the book. This edition is bigger than previous ones and the publishers must have considered using two volumes. Inevitably in a multi-author book, there is a good deal of repetition. Therefore, this is a book for reference rather than an easy read. In general terms I found much of the style dry, and occasionally there is relatively little hard clinical advice to follow up the excellent and thorough science. Many of the illustrations appear rather old and indeed existed in the 1990 edition. This does not give the impression of a "state of the art" book.

The book is divided into four parts: (1) basic principles, (2) general approach to paediatric anaesthesia, (3) clinical management of special surgical problems, and (4) associated problems, including a chapter on malignant hyperthermia and systemic disorders. This latter chapter on systemic disorders is well worth reading, but does not provide a comprehensive reference of the more unusual disorders. There is good advice on asthma and the runny nose. Relatively up-to-date topics (e.g. laryngeal mask, propofol in intensive care and extradurals) are covered but some chapters have few recent references. The chapter on respiratory physiology by Motoyama is hard work, but is a comprehensive review The chapter on pain and an updated chapter on regional anaesthesia are valuable. For bedtime reading, Smith has included a contribution on history. One topic that is consistently covered inadequately in textbooks is the use of ventilators in infants during surgery, and this book is no exception.

However, in general these criticisms are minor, and although there is too much depth for the examination candidate, this is undeniably an excellent reference for all those who encounter children in anaesthetic practice.

*I. Wilson*

*FRCA: Passing the Primary Examination.* H. WILLIAMS, M. HASAN, M. BRUNNER AND N. ROBINSON. Published by Butterworth-Heinemann, Oxford. Pp 150; indexed. Price £14.99.

The examination system of the Royal College of Anaesthetists is designed to assess the worth of anaesthetists to attain specific standards rather than to test if candidates can "jump through hoops". Some areas of this book may suggest that more of the latter occurs that the former. The introduction claims that the book is set to the examination standard, but how this was achieved when compiled before the inception of the new primary examination is unclear.

The book comprises five chapters. The first two cover the examination and the syllabus, information which is available free from the College. Chapter 3 represents 50% of the bulk of the book and is composed of MCQs arranged first in subjects and then in a mixture to mimic an examination paper for practice. Many of the questions look familiar but may provide only false reassurance to candidates for the new primary examination. There is some useful advice on examination technique. Chapter 4 concentrates on the viva exams but comprises only 12% of the book. The style here is somewhat colloquial and some may find it flippant for what is essentially a serious subject for prospective candidates. There is more than one mention of Arsenal football club for example! There are some perhaps misleading assertions, familiar to examiners. Chapter 5, by the authors' admission, is new ground, but they provide a brave attempt at some guidelines and principles in 20 pages.

The introduction to the book states that it is "not just another MCQ book". This is true, but the thirst for such texts by future trainees will ensure that it joins others in that mould.

*D. Fell*

*Difficulties in Tracheal Intubation.* I. P. LATTO AND R. S. VAUGHAN. Published by WB Sanders, London. Pp. 393; indexed; illustrated. Price £40.00.

The first edition of this textbook was an important and relatively unrivalled contribution. It served to focus attention on a subject that had perhaps been taken for granted. Furthermore, it probably inspired many interested parties into making their own contributions. Over the decade since it first appeared, there has been a major explosion of knowledge, and important, interesting differences in approach remain not only across the Atlantic but also between the centres of learning generally. There is also an emerging rivalry with alternative texts. The rapidly expanding knowledge base is not easy to keep up with and difficult to summarize.

While there is a new chapter on intubation for cervical spine injuries it seems unfortunate that there is still no room for major ENT and maxillofacial problems which remain the most technically difficult situations. Some mention of subglottic pathology is at times painfully absent because of an apparent assumption that a tracheostomy or cricothyrotomy will solve airway problems difficult to overcome by other means. There is more space devoted to the difficult airway than before, but it is perhaps unexpected that the problematic airway management for sleep apnoea and related problems, and also the vexed questions on the appropriateness or otherwise of surgical interventions are not included. Understanding of the mechanisms in difficult laryngoscopy has advanced but this receives almost no coverage. One of the continuing problems for studies of predicting difficulty and comparative laryngoscopy has been the failure to standardize methodology and again this might have been referred to when summarizing the current position.

More detail is proposed for the content of teaching programmes for airway management and training for fibreoptic intubations, which is obviously helpful. On the other hand, perhaps what is also required is some advisory knowledge about what should be considered appropriate to attempt and when. In many institutions in the UK it would appear to be the case that for quite difficult elective cases two consultants are often present to cooperate and ensure optimal patient care. It is probably also the case that in practice, diagnosis and appropriate investigative imaging for such elective cases receive more attention than the text generally might imply. There are new large sections to outline the impact of the laryngeal mask airway and the Combitube. Management algorithms for various situations are dealt with sympathetically so as to encourage those who might feel they have a lot to offer compared with others who just want to make sure that they understand the limitations of their abilities so as not to burn bridges. The inclusion of a "legal implications" chapter is an interesting innovation for a UK text and should at least encourage healthy discussion.

Despite the above criticisms this second edition should serve as a focus for further stimulating thought and encouraging research in these important clinical areas. Obviously with rival purchases in a fairly specialist area, anaesthetists need to decide which is the most useful to them. It seems very unlikely that a text of similar size from other UK only authors is imminent.

*P. Charters*

*Patient Safety in Anesthetic Practice.* R. C. MORELL AND J. H. EICHHORN (editors). Published by Churchill Livingstone, New York. Pp. 509; indexed; illustrated. Price £50.00.

This text reviews anaesthesia patient safety endeavours which have occurred within the last 15–16 yr and which are pertinent to current practice. As stated by the editors in the preface, "great efforts have been made to ensure accuracy and to minimize contradictions and redundancy". The multi-author approach is therefore essential in order to provide concise, clearly presented, evidence-based contributions from early workers and leaders in this field.

There are 20 chapters, starting with a brief introduction to the approach to patient safety in the 19th and early 20th centuries. The next four chapters address the need to understand the complexity of anaesthetic and patient monitoring equipment; the one on medical gas vacuum systems used in the USA and therefore subject to different safety regulatory codes, guidelines and standards from those in the UK, is still very informative and the case orientated approach to electrical safety in the following chapter is effective in imparting crucial facts. The chapters on the anaesthetic machine and the advantages and limitations of pulse oximetry and capnography discuss the checks required to ensure the reliability of sophisticated equipment which provide and monitor perioperative care. Misuse or malfunction issues are addressed clearly. The next sections review risk factors in the management of paediatric, adult and pregnant patients; remarkably little is written on the elderly but the impact of anatomical and physiological changes in the pregnant patient is discussed. Information relating to drug safety and patient positioning, together with regional anaesthesia considerations, precede examination of the anaesthetic safety concerns of the recovery unit and particular problems within the intensive care unit, with emphasis on events, safety considerations and standards within these two environments. The case for increasing patient safety through standards and guidelines, practice parameters and algorithms is well argued and supported in further chapters, and the place of the automated anaesthesia record is put into perspective with today's practice.

Overall, this text would be worth buying for the last four chapters alone. These relate to the increasing use of simulators and other training devices in crisis resource management and an authoritative review of the problems known or believed to affect the performance of anaesthetists. The environmental and occupational hazards encountered by anaesthetic personnel are discussed in the penultimate chapter, while the last is an interesting account of adverse events, malpractice claims and the litigation process. The figures and tables are clear and the index logical.

Although written with American practice in mind, this text addresses issues and questions which are relevant to all anaesthetic practitioners in the UK. It is absorbing reading and if not on every anaesthetist's bookshelf it should be found a place in every anaesthetic department where both trainers and trainees can easily access the wealth of commonsense contained within its covers.

*J. Lumley*

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*"I would have everie man write what he knowes and no more."*—MONTAIGNE

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## EDITORIAL I

### The expanding role of simulators in risk management

Anaesthetic simulators have been in the news since the 1960s,[1] but the development of theatre-type simulators (TTS)[2 3] in which much of the operating room setting can be reproduced, including the interaction of various personnel, is a feature of only the last decade. Gravenstein[4] has written that the practice of anaesthesia calls for two virtues, compassion towards patients and respect for co-workers, and four abilities, comprehension of facts, grasp of concepts, manual skill and quick response. In several centres in the USA and Canada,[5] in Japan and in continental Europe, there are established simulator training centres in which, to a varying degree, each of these qualities can be developed and tested. The use of simulators can be extended, in some instances, to traumatology, other acute medicine and basic science training.

In the UK the first TTS was inaugurated at Bristol on January 27, 1997. There was extensive media coverage of the event so that public awareness of its possibilities for greater safety has been boosted significantly. The Bristol development, which may soon be followed by others, owes something to an initiative taken by the Council of the Royal College of Anaesthetists, in the early 1990s, who commissioned a report from Professor John Norman and Dr David Wilkins,[6] greatly assisted by several North American colleagues, notably in Gainesville and Boston.

TTS simulators are expensive facilities, some costing in excess of £1m per year. Elements of the total cost include physical accommodation, cost of patient simulator and associated computers and furnishings for the operating room. Accommodation is also needed for screened-off monitoring of events and for induction and debriefing sessions. Human resources include the need for instructors who combine charisma with teaching and, probably, counselling skills. Thespian leanings together with a reasonable command of the complex technology are also important, arguably essential. Not every anaesthetist has all the necessary attributes!

Is the cost justified? Probably no one can give a precise answer because the balance sheet includes not just financial considerations but possible saving of life, and potential for further development of simulation in the future. Simulators may improve and expedite skills training, perhaps especially in countries such as the UK where the anticipated period of training in medical specialties is expected to reduce, and where hospital management pressures for more efficient throughput result in shorter periods of hospital stay with associated reduced clinical access for the trainee.

Simulators could be used for entirely different purposes in relation to the increased public and professional interest in assessing the adequacy of a doctor's clinical performance.[2] Clearly it is important for the specialties to have an agreed, honest and convincing position on this. Whatever happens in the future, to turn away from simulators, or ignore an aspect which obviously some doctors would see as a threat, is not an option.

Some simulator centres include facilities for the display and use of a variety of other training devices, for cardiopulmonary resuscitation, fibre-optic endoscopy and also computer screen-based simulators (SBS). Asbury has pointed out the fact that SBS devices are particularly useful for learning alone or at home because they are obviously relatively mobile.[3] One example which has enjoyed some acclaim in the UK was developed by Byrne, Hilton and Lunn.[7] In this issue of *British Journal of Anaesthesia* there is an interesting account of the use of this device to examine the accuracy of reporting of simulated critical incidents.[8] Eleven anaesthetists in training were individually exposed to a simulated pattern of critical incidents. The purpose was to compare the anaesthetist's written accounts of events after the incidents had been completed with what was presented to them in the first place, and a video tape of their overall performance. The authors of the report were satisfied that the simulation was considered realistic by all participants, and that participants were acceptably experienced to take part. The study suggests that (some) anaesthetists are quite likely to record events according to their perception of the type of complication they believe to be developing. The authors state in their conclusion: "The observed results are more consistent with the recall of patterns or schemata rather than actual events". Such findings may not surprise everyone in the anaesthetic community. Indeed those who remember puzzle sections in childrens' magazines will feel they have always known that patterns of recognition are highly prone to preconception. Within the anaesthetic literature such phenomena have been identified previously.[9 10]

Dr Byrne and Professor Jones are correct in sounding a warning about the analysis of critical incidents and the need for measures to ensure validation of the information that is collected. But there are other important considerations. The reliability of recorded data when more than one doctor is involved in managing a patient and "hand over" strategies are allowed may be poorer than we like to believe. One might also ask if an anaesthetic record which becomes a very central piece of evidence in a court of law is all that some might think. And (craving the Editor's indulgence) do we always read the truth in clinical case reports? These may not be helpful questions, because in the absence of a "black box" recorder there is no obvious answer. Perhaps, of course, simulators can help anaesthetists in their formative years to learn some of the tricks of the mind, and operate in a more disciplined manner.

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## EDITORIAL II

# Meningitis after spinal anaesthesia

Bacterial meningitis is a common and devastating illness that presents as a medical emergency requiring considerable diagnostic and therapeutic skills. Mortality is high and even those who recover may suffer a variety of permanent neurological sequelae. Because lumbar puncture (for whatever purpose) bypasses all the natural defence barriers of the central nervous system, it is clear that it carries at least the theoretical risk of introducing infection and causing meningitis. Two routes exist for such infection to reach the CSF. First, failure of aseptic technique could result in the introduction of exogenous organisms into the cerebrospinal fluid. Second, bacteria in the patient's blood at the time of lumbar puncture may gain access to the subarachnoid space because of microscopic bleeding caused by insertion of the needle.

Fortunately, there is good epidemiological evidence that the frequency of meningitis after lumbar puncture is no greater than in the ordinary population. Even in bacteraemic patients the incidence of meningitis after diagnostic lumbar puncture is not significantly different from the expected spontaneous rate.[1] Furthermore, there were no cases of CSF infection in the classic prospective study of 8460 patients undergoing 10 098 spinal anaesthetics performed by Dripps and Vandam.[2] Many of these patients underwent obstetric or urological procedures and were therefore at risk of bacteraemia, the incidence of which has been estimated at 3.6–7.2% after normal delivery.[3] Higher rates might be expected in patients with obstetric complications such as chorioamnionitis or retained placenta, but two retrospective reviews of 27 000 and 505 000 patients who received extradural block in labour revealed only two with infective sequelae.[4 5]

This safety record may be attributed in part to the practice of prescribing antibiotics in such patients to reduce both maternal and neonatal morbidity.[6 7] In an attempt to evaluate this, Carp and Bailey performed a series of studies in which lumbar puncture was performed in bacteraemic rats.[8] Only those animals with a circulating count of *Escherichia coli* (*E. coli*) of greater than 50 colony forming units per millilitre at the time of lumbar puncture developed meningitis. When lumbar puncture was performed in animals without bacteraemia, or in those given a dose of gentamicin, there were no episodes of meningitis. Although *E. coli* rarely causes meningitis the study does support current clinical proposals. Chestnut recommends that spinal or extradural block can be performed in selected infected patients with the proviso that appropriate antibiotic therapy has begun and that the patient has shown a positive response.[9] An antibiotic with a broad spectrum of activity seems advisable given the suggestion that meningitis after recent spinal anaesthesia is often caused by unusual or nosocomial infection.[10] Such therapy might serve only to delay the onset of symptoms, but when meningitis occurs 25 days after a spinal anaesthetic (for a haemorrhoidectomy) it does seem more likely that it is coincidental.[11]

Antibiotic therapy is usually introduced very early in any patient with meningeal symptoms, particularly if there are other signs of infection or a potential "aetiological factor" such as lumbar puncture for spinal anaesthesia. When purulent CSF is obtained from such patients, but no organisms are grown on culture, there is often an assumption that the antibiotic has inhibited bacterial growth. However, it is important to remember that bacteria are not the only cause of meningitis. The viral condition is generally much more benign, but may be caused by a wide range of organisms, and Coxsackie B infection has been described after extradural block on at least one occasion.[12] Genital HSV infection occurs in 0.5–1% of pregnant women and HSV meningitis has been reported in 8% of those with the primary infection.[13] It is a matter of mere epidemiological coincidence that some patients who have received spinal or extradural block could develop this infection.

However, most cases of meningitis after central nerve block are probably aseptic in origin. Fifty years ago aseptic meningitis was not an uncommon complication of spinal anaesthesia and by 1947 more than 100 cases had been described in the literature and an incidence of 0.26% was quoted in a summary report of approximately 46 000 spinal anaesthetics.[14 15] However, the incidence declined dramatically during the 1950s after a series of studies that had implicated chemical contamination of the CSF as the cause. It was shown in 1937 that this could result in meningeal irritation and animal studies showed that a whole range of detergents and chemicals could produce symptoms and histological changes consistent with aseptic meningitis.[16–18] Recognition of these factors led to improvements in technique and equipment and these have reduced markedly the incidence of problems, although sporadic case reports still emphasize the need for attention to detail.[19–21]

Another important, but much less widely appreciated, cause of aseptic meningitis is systemic drug administration. Drug-induced meningitis has been reported after non-steroidal anti-inflammatory agents, antimicrobials, ranitidine, carbamazepine and azothiaprine. In 1992, Marinac summarized 31 cases after ibuprofen alone in a literature review.[22] The syndrome is more common in females with underlying autoimmune or collagen vascular disorders, but is occasionally reported in normal individuals, and is presumed to be an acute hypersensitivity reaction. There are some immunological data to support this hypothesis.[23 24] Signs and symptoms typically appear a few hours after drug ingestion, but may be delayed by weeks. In addition to the usual features of meningitis there may be periorbital oedema, conjunctivitis, hypotension, parotitis, pancreatitis, lethargy, diplopia, seizures and confusion. Fever is common. The CSF picture varies greatly, but there is generally polymorphonuclear pleocytosis, increase in protein concentration and normal glucose. Symptoms worsen with continued drug administration, but most patients recover fully in a few days after the offending medication is stopped. Definitive diagnosis requires re-administration of the drug to the patient.

Irritation and inflammation of the meninges must be accepted as a potential complication of spinal anaesthesia. Perhaps the greatest advantage of the technique is that only a tiny dose of drug is required to produce a major degree of block, the main reason being that all the barriers surrounding the spinal cord and nerve roots are bypassed by the injection and the drug reaches its site of action easily. However, all the natural protection of the CSF is circumvented also. As long as equipment and drug solutions manufactured to modern standards are applied with a sound aseptic technique, the incidence of complications should be very low and the occasional case of meningitis is likely to be coincidental. However, every case should prompt a thorough consideration of all possible aetiological factors and this must include the equipment and technique used. When there is no obvious bacterial infection the possibilities of viral infection, chemical contamination and drug-induced meningitis must each be investigated. The latter is particularly important given that two groups of drugs used widely in anaesthesia (NSAID and $H_2$ blocking agents) have been shown to cause the condition. We have traced five cases of meningitis after dural puncture in the recent medical literature[19–21 25 26]; four of these were aseptic in nature but no intercurrent drug history was given and the possibility of drug-induced meningitis was not raised.

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CLINICAL INVESTIGATIONS

# Inaccurate reporting of simulated critical anaesthetic incidents

A. J. BYRNE AND J. G. JONES

## Summary

Eleven anaesthetists completed a simulated anaesthetic which was deliberately complicated by a slow progressive bradycardia followed by an episode of severe bronchospasm. After the simulation, each anaesthetist was asked to complete an anaesthetic chart and a critical incident report. Considerable discrepancies were found between the anaesthetists' written accounts, a videotape of their performance and actual data from the simulator. During the simulations, all of the anaesthetists reacted appropriately and treated their "patient" successfully but their written accounts showed a tendency to record "typical" rather than actual events and to ignore events not consistent with their final diagnosis. Only four anaesthetists mentioned bradycardia in their written description and none accurately described the changes in arterial pressure during the episode of bronchospasm. The findings are in keeping with other studies which suggest that people record events as "schemata" rather than as collections of discrete facts. These results have significant implications for those involved in the teaching of anaesthesia and in the analysis of critical incidents. (*Br. J. Anaesth.* 1997; **78**: 637–641).

**Key words**
Anaesthesia, audit. Computers, simulation Model, computer simulation. Anaesthetist, training.

The Anaesthetic Computer Controlled Emergency Situation Simulator (ACCESS)[1] has been used over the past 3 yr to provide basic training for junior anaesthetists and to assess their ability to deal with critical incidents. The simulator consists of a resuscitation manikin in place of a patient, an anaesthetic machine/ventilator and computer simulated monitors. The anaesthetic machine is a basic "Boyles machine" complete with TEC3 vaporizer, which appears to function normally, but which has been modified to avoid the use of real volatile agents or nitrous oxide. A Manley MP3 ventilator was used during this study. The monitors provide information on non-invasive arterial pressure, pulse oximetry, ECG, inspired oxygen concentration and end-tidal carbon dioxide concentration. Simulations are presented as clinical scenarios which test the ability of the trainee to deal with a specific emergency. The simulations are realistic, as judged by those who have taken part,[1] and require appropriate manual responses to be performed by the trainee, for example, hand ventilating the lungs of the "patient" or injecting drugs.

During previous training sessions it was noticed that trainees often seemed to have misinterpreted the data presented and, when asked to describe their actions, their descriptions often contained factual inaccuracies. However, these inaccuracies were usually plausible and consistent with their stated final diagnosis. For example, if they failed to notice a gradual bradycardia, they often stated that heart rate had been normal initially and had then changed suddenly.

This study was designed to test if the observed anomalies arose from the anaesthetist misunderstanding the simulation, from the anaesthetist's inability to manage the simulated critical incident, or if the problem lay in the ability of the anaesthetist to remember events accurately.

## Methods

Eleven trainee anaesthetists, with 3–8 yr clinical experience, volunteered to take part in a single simulation, with no opportunity for trial runs or practice. None had used ACCESS previously and they were told only that their performance would be evaluated during a standard simulated anaesthetic. The same investigator gave each anaesthetist a verbal introduction to the simulator lasting 3–4 min.

During each simulation, the investigator acted as a helpful aide, to provide physical assistance for any task, but not to provide useful diagnostic or therapeutic information. However, the investigator did answer questions related to the simulation, for example, if cyanosis was present or if the breath sounds had altered in character.

Each anaesthetist was introduced to the simulation as if taking over a routine anaesthetic from a colleague. They were shown a preoperative assessment form and were told about the anaesthetic technique being used. The "patient" for each anaesthetist was based on a real case and was young and healthy. The "operation" was an open reduction and internal fixation of an ankle fracture, the patient having had a local anaesthetic ankle block and been

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paralysed, the trachea intubated and the lungs ventilated 20 min before the anaesthetist taking over the case. Drugs "used" were thiopentone, vecuronium, fentanyl and bupivacaine. Each anaesthetist was allowed to ask questions and to check the settings on the ventilator, anaesthetic machine and monitors.

The simulation was started as soon as the anaesthetist was familiar with the situation and ended when the "patient" had been treated correctly and was stable. Each entire episode was videotaped for later analysis. At the end of each simulation, each anaesthetist was asked to immediately complete an anaesthetic chart and a critical incident report, covering the period of simulation. They were not asked questions about any specific event, but were simply asked to record the simulated events in free text, as if it were a real case. The computer printed out a timed list of all significant events and the heart rate of the "patient" during the period of each simulation. This printed output was not made available to the anaesthetist.

Each simulation contained two critical incidents: phase one, a bradycardia and phase two, an episode of bronchospasm induced by a dose of antibiotic. During phase one, heart rate started at 80 beat min$^{-1}$ and decreased in a linear manner, by 10 beat min$^{-1}$ every 3 min, with only minor random variation. There was no consistent change in arterial pressure. It was expected that at some point the anaesthetist would administer a dose of anticholinergic drug to correct the bradycardia. When this dose had been given and bradycardia corrected, the simulation moved into phase two. The purpose of the first phase was to compare the actual change in heart rate (from the simulator printout) with the change documented on the anaesthetic chart and the anaesthetist's perception of events from their written account.

At the start of the second phase, the anaesthetist was told that the surgeon had requested that a dose of i.v. flucloxacillin be given. As soon as the anaesthetist administered some of the flucloxacillin, airways resistance increased markedly, simulating an episode of bronchospasm. This was manifest by the Manley ventilator being unable to deliver the set tidal volume. Arterial pressure remained normal for two further readings (at least 2 min) and then rapidly became unrecordable. This simulated a reduced cardiac output secondary to air trapping and was based on a real critical incident. It was expected that the anaesthetists would administer i.v. fluids and adrenaline, although any reasonable combinations of treatment would have resulted in the "recovery" of the "patient". For example treatment with salbutamol, aminophylline or adrenaline, in appropriate doses, would all result in a reduction in airways resistance. When these treatments had been given and the "patient" had stabilized, it was planned that the simulation would be terminated. The purpose of this phase was to observe if the anaesthetists would be aware of the changes in arterial pressure, if these changes would influence diagnosis/treatment and if the information would be recorded in their written account.

The realism of the simulations was assessed by asking the anaesthetists to answer two questions, using a linear analogue score from 1 (unrealistic) to 10 (realistic), in response to the questions "How do you rate the realism of the simulation?" and "How do you rate the realism of your responses to the simulation?". This assessment was performed to ensure that ACCESS was providing a level of realism.

## Results

All anaesthetists responded appropriately to the simulation; all "patients" were treated appropriately and all simulations were continued to a successful conclusion.

### RESPONSES TO SIMULATED BRADYCARDIA

In the first phase, all 11 anaesthetists diagnosed bradycardia and administered an adequate dose of anticholinergic, either atropine 300–600 μg or glycopyrronium 200–400 μg. However, three anaesthetists failed to document bradycardia and two failed to record administration of a drug on their anaesthetic chart.

In the critical incident report, only four of the 11 anaesthetists mentioned bradycardia, and these comments are reproduced in table 1. Only the first anaesthetist described the simulation accurately, with the next two anaesthetists being less specific. Anaesthetist No. 4 described the actual, gradual onset of bradycardia as a single rapid episode, with associated hypotension (which was not present). Anaesthetist No. 5 ignored the bradycardia and described an episode of hypotension. (Actual systolic arterial pressure values shown, at minute intervals, were: 102, 90, 88, 96, 98, 115, 101, 92, 100, 104 and 110 mm Hg.)

Subsequent inspection of the anaesthetic charts confirmed that all 11 anaesthetists were unable to

*Table 1* Expected and observed descriptions of phase I of the simulation by anaesthetists (six anaesthetists did not describe this phase)

| | |
|---|---|
| Expected | There was a gradual decline in heart rate from 80 to 35 beat min$^{-1}$ over the first 15 min, otherwise the patient was stable. |
| Anaesthetist (No.) | Reported events |
| (1) | "... gradual decline in HR noted No change in ECG. No change in BP. No cause evident." |
| (2) | "One episode of bradycardia during GA, responded to atropine (300 μg) otherwise CVS +$O_2$ Sats >96%." |
| (3) | "Approximately 40 min into the procedure, which was otherwise unremarkable other than bradycardia (sinus) to 42 beat min$^{-1}$. $R_X$ atropine." |
| (4) | "The first 30 min of anaesthesia and surgery was stable. The "patient" then developed a bradycardia, with the heart rate decreasing to about 30 beat min$^{-1}$. Arterial blood pressure was reduced but still maintained within acceptable limits." |
| (5) | "Initially everything was fine, then BP started to slowly drop from 120 to 90 systolic. Responded to Hartmann's 1L." |
| (6–11) | No comment made about bradycardia |

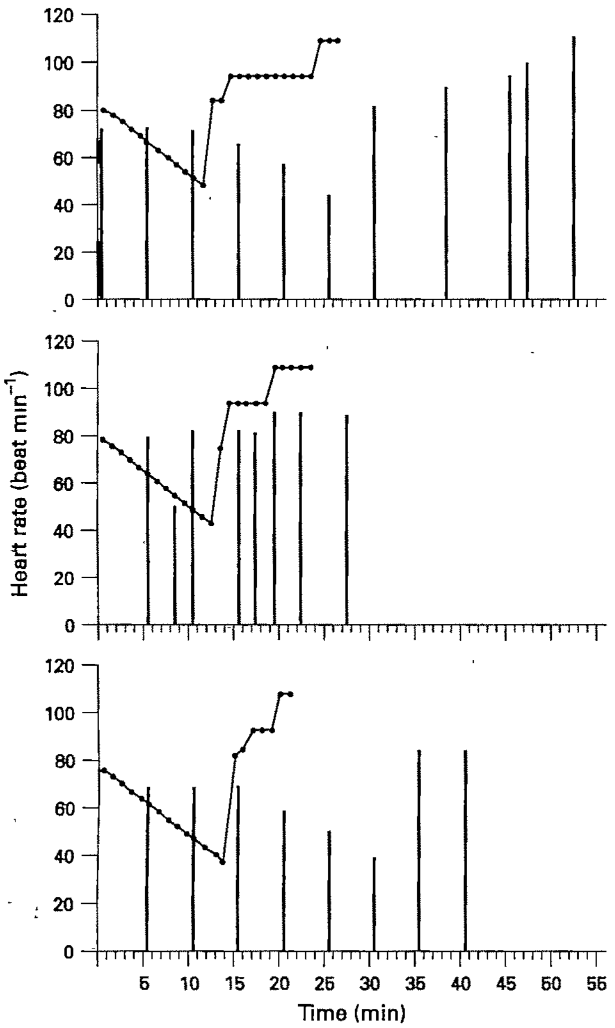

*Figure 1* Actual and recorded heart rates for anaesthetists Nos 9, 10 and 11.

record accurately the simulated events or their time scale. Figure 1 shows examples of actual heart rates plotted on the same scale as those recorded by the anaesthetist. Overall, subjects tended to record an initial stable period, followed by a brief bradycardia, rather than a gradually evolving bradycardia. The anaesthetists' charts often showed a time scale twice as long as the real events.

RESPONSES TO SIMULATED BRONCHOSPASM

All 11 anaesthetists described the second phase of the simulation, but there were significant differences between actual and recorded events.

*Table 2* Expected and observed descriptions of phase two of the simulation by anaesthetists

| Expected | After a test dose of flucloxacillin, patient developed bronchospasm. Arterial pressure was initially normal but decreased rapidly after 2 min. Patient responded to i.v. and adrenaline. |
|---|---|
| Anaesthetist | Reported events |
| (1) | "following i.v. fluclox, *P*aw increased such that the Manley was ineffective. A diagnosis of anaphylaxis was made, $Fi_{O_2}$ to 100%. IPPV by bag. Auscultation, widespread wheeze bilat. Adrenaline 100 µg given i.v with quick result. As compliance improved => Manley. 1% ISO throughout. No desaturation. No hypotension." |
| (2) | "On administering flucloxacillin 50 mg during CVS collapse, airway (*P*) increased + Sats decreased to 91%." |
| (3) | "I was then asked to administer flucloxacillin which I did i.v. Over the course of the next few minutes, the 'patient' dropped his $Sa_{O_2}$% to 92–93%, developed bilateral bronchospasm, and also progressively dropped his blood pressure." |
| (4) | "'patient' developed bronchospasm + hypotension in response to i.v. flucloxacillin " |
| (5) | "Asked to give antibiotic. No Hx of allergy. Diluted flucloxacillin 1 g in 10 ml. 2 ml test dose—bronchospasm, hypotension." |
| (6) | "Immediately after flucloxacillin solution 1 ml—tight bronchospasm with ventilator unable to deliver volume ... Minimum $Sa_{O_2}$ 92%, $ETCO_2$ to 3.3 kPa. BP always strongly palpable—minimum recorded 89/56 (although BP machine malfunctioned for 2 min during event)" |
| (7) | "Flucloxacillin 1 g i.v. Events: (chronologically) (1) bronchospasm, (2) no BP recorded, (3) back to normality" |
| (8) | "After giving test dose of fluclox. 'patient' became difficult to ventilate and was wheezy with very little air entry suggesting severe bronchospasm." |
| (9) | "Test dose of 50 µg given. 'Patient' developed bronchospam evident by increased *P*aw and decreased AE within 30 s. No response to salbutamol via ETT. Subsequent hypotension (no BP on Dinamap) but faint carotid pulse." |
| (10) | "1-ml test dose given > bronchospasm > hard to ventilate with halothane, i.v. salbutamol + adrenaline + fluids." |
| (11) | "Bronchospasm + 'anaphylactic' hypotension 2° to i.v. fluclox ... Min BP 52/mm $Sp_{O_2}$ 92%" |

*Table 3* Assessment of realism by anaesthetists, using visual analogue scale (0=unrealistic, 10=realistic)

| | Median score | Range |
|---|---|---|
| How do you rate the realism of the simulations? | 8 | (6–8) |
| How do you rate the realism of your responses to the simulation? | 7 | (5–8) |

In their critical incident reports (table 2), none of the anaesthetists commented that arterial pressure had been normal for 2 min after bronchospasm had started. Only two anaesthetists (Nos 7 and 9) correctly described the actual sequence of events. Analysis of the videotapes however, showed that most of the anaesthetists had looked at the arterial pressure reading soon after bronchospasm had started. Seven of the 11 anaesthetists either stated that arterial pressure was normal and/or increased the inspired concentration of volatile agent, indicating that most were aware of the initially normal arterial pressure. For example, anaesthetist No. 2 stated "Sats OK, BP OK" just before starting to treat the bronchospasm with aminophylline. Yet the same anaesthetist described, in the written account, the hypotension ("CVS collapse") as occurring before or at least at the same time as the bronchospasm.

The answers to the questionnaire (table 3) showed that the anaesthetists thought that the simulations were realistic.

## Discussion

This study has shown that a group of trainee anaesthetists treated a simulated "patient" in a realistic manner. However, their written accounts of events were influenced heavily by their own final diagnosis, with events being altered or omitted to fit with this diagnosis.

### SIMULATED BRADYCARDIA

The results from phase 1 showed a tendency for the anaesthetists to ignore any events which they perceived as not being directly related to their "main" problem, in that seven of 11 did not report that bradycardia had occurred. They also showed a tendency to "normalize" events. A gradual decrease in heart rate is unusual, but this was mentioned by only one anaesthetist who wrote, "No cause evident". Anaesthetists Nos 2, 3 and 4 mentioned that bradycardia had occurred. The implication is that the anaesthetists were not able to remember individual values for each of the variables shown, but were recording events as complete episodes. This view is reinforced by the recorded values on the anaesthetic charts (fig. 1) which tended to show an initial period of normal heart rate followed by sudden bradycardia. In other words, the first phase of the simulation had been remembered as two discrete episodes, an initial episode of normality, followed by an episode of bradycardia. When writing about the events afterwards, values for heart rate and arterial pressure were obtained from their own mental models of those events.

This may also explain why anaesthetist No. 5 reported a single reading of systolic arterial pressure of 88 mm Hg as an episode of hypotension. This was only a small decrease from the real initial value of 102 mm Hg. However, he reported an initial value of 120 mm Hg, that is a "normal" arterial pressure, which would make a subsequent systolic pressure of 88 mm Hg more significant. The next reading of a systolic arterial pressure of 115 mm Hg may have indicated that the i.v. fluid had been successful in treating the "hypotension", reinforcing the diagnosis. A later value of 90 mm Hg was then ignored.

### SIMULATED BRONCHOSPASM

During phase 2 all anaesthetists responded appropriately to the increased airways resistance and appeared to be aware of the normal arterial pressure initially and to make a diagnosis of isolated bronchospasm. Subsequently, when arterial pressure began to decrease, the anaesthetists seemed to change the diagnosis from bronchospasm to a generalized anaphylactic reaction. Then, when their treatment began to be effective and heart rate and arterial pressure began to return to normal, the new diagnosis of anaphylaxis with cardiovascular collapse was reinforced. Therefore, the episode was remembered as an episode of anaphylaxis and any inconsistent information was subconsciously suppressed, or not remembered.

Within the specialty of anaesthesia, an accurate record is of prime importance and errors have tended previously to be described in terms of inattention or misdiagnosis. This study tested anaesthetists during daylight hours, without the distractions of bleeps, telephone calls and audit forms. The short period of the study also implied that boredom was unlikely to have been a factor. All "patients" were treated correctly and the anaesthetists appeared to have few difficulties in understanding the data presented by the simulator. Although an anaesthetist "taking over" a case half way through may not be regarded as "best practice", trainee anaesthetists are often asked to take over the care of patients for short periods. This is usually regarded as acceptable provided the incoming anaesthetist is briefed correctly, as was the case in this study. The conclusion is therefore that the errors observed were caused by problems with the recall of events by the anaesthetists.

The problems described here have been observed in other fields such as aviation and the nuclear power industry and have been the subject of considerable research.[2 3] In particular, our limited capacity to retain numerous discrete elements of data[4] and the tendency of subjects to act on the present value of a variable rather than the trend[5] have been demonstrated. The observation that memories are stored as typical "patterns" or "schemata" has been described as far back as 1934.[6] The relevance to anaesthetic practice was described by Allnutt in 1987, "Thus, with the highest integrity, we soon start reporting not what happened, but *what must have happened*" (authors italics).[7]

These problems have several important consequences for those analysing critical incidents. First, if anaesthetists are taught to deal with a list of well defined emergencies, with their attendant signs, symptoms and solutions, it is likely that they may try subconsciously to make any real emergency "fit" one of this list. Any record of the event may then resemble the textbook example more than the real events, with the consequence that vital details may be obscured. In particular, complications or associations which have not been recognized previously may continue or go unreported. Second, any aspect of the real event which was unusual or incompatible with the diagnosis made tends to be ignored or reduced in value. Any details recorded tend to support the final diagnosis.

This study can be criticized for not using real cases and for the analysed records not having been made contemporaneously. However, the anaesthetists reacted appropriately to the simulations and rated the experience as realistic. This is reinforced by the observation that one anaesthetist administered a dose of neuromuscular blocker to stop a plastic resuscitation manikin from "coughing". Although the records were made immediately after the event and not at the same time, it is unlikely that during a real critical incident anaesthetists would have the time to fill in an anaesthetic chart or to review trends on a monitor. Therefore, during a critical incident, when decisions have to be made, anaesthetists have to rely on their own memory for details of recent events, and that is what has been tested here.

Finally, our knowledge of anaesthetic emergencies, their diagnosis and treatment has largely been built up from analysis of critical incident forms. This study indicates that the information derived from that source may not reflect actual events. Although some anaesthetic machines are capable of providing detailed case records, monitors may not provide accurate readings during a sudden catastrophic event such as anaphylaxis. In addition, they do not record all the actions of the anaesthetist. Cases where the automated record differed substantially from the events perceived by the anaesthetist may cause difficulties for both trainers and those seeking to defend against litigation. Automated recording of monitoring and videotaping of the anaesthetic would seem to provide the best solution, but this is unlikely to receive widespread acceptance and has significant cost implications. Overall, the most immediate solution is for those involved with the analysis of critical incidents and in the debriefing of the participants to be aware that written and verbal accounts of events may be inaccurate. In addition, trainers need to ensure that anaesthetists are aware of the limitations of their perception. In particular, it is vital for anaesthetists to constantly re-check diagnoses and assumptions as a critical event develops.

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# Propofol and bradycardia: causation, frequency and severity

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## Summary

As part of the development of a model for the study of adverse events, we have investigated the risk of bradycardia with propofol. A systematic search for any type of report, published and unpublished, was made to review the evidence that propofol increases the risk of bradycardia, asystole and death from bradycardic events. Quantitative and qualitative analyses of data with different strengths of evidence were performed. Sixty-five published and 187 spontaneous reports to drug monitoring centres described with different strength of evidence a biological basis for propofol-induced bradycardia, 1444 bradycardias, 86 asystoles and 24 deaths. In controlled clinical trials, propofol significantly increased the risk of bradycardia compared with other anaesthetics (number-needed-to-harm 11.3 (95% confidence interval 7.7–21)). In paediatric strabismus surgery the number-needed-to-harm was 4.1 (3–6.7). One of 660 patients undergoing propofol anaesthesia had an asystole. The risk of bradycardia-related death during propofol anaesthesia was estimated to be 1.4 in 100 000. Data from the phase IV study of propofol did not agree with data from controlled studies. Propofol carries a finite risk for bradycardia with potential for major harm. Study of adverse events should be made with systematically searched data and, in contrast with study of efficacy, not restricted to randomized, controlled trials. (*Br. J. Anaesth.* 1997; **78**: 642–651).

**Key words**
Anaesthetics i.v., propofol. Heart, heart rate. Complications, bradycardia. Complications, asystole. Anaesthesia, audit.

Propofol has been available since the early 1980s. It has gained widespread popularity because it is thought to have specific advantages compared with other anaesthetics, such as favourable kinetics,[1] smooth induction characteristics, a recovery profile with a low incidence of adverse effects[2] and non-hypnotic therapeutic properties.[3] It was suggested that the excellent haemodynamic state was of particular use in paediatric patients.[4]

During propofol anaesthesia a low heart rate may occur despite decreased arterial pressure.[5 6] Absence of reflex tachycardia may be considered beneficial because it is not associated with an increase in myocardial oxygen consumption. However, observational reports on profound bradycardia and asystole with the use of propofol in healthy adult patients, despite prophylactic anticholinergics, have been published repeatedly.[7–9] Severe, refractory and fatal bradycardias in children in the ICU have been observed with long-term propofol sedation.[10–12] The question has been raised of when, if ever, case reports become good enough evidence on which to base practice.[13]

There is now strong evidence from a meta-analysis of all relevant randomized controlled trials (RCT) that propofol anaesthesia, compared with other anaesthetics, increases substantially the incidence of the oculocardiac reflex (OCR) in paediatric strabismus surgery despite the use of prophylactic anticholinergics.[14] The OCR, a trigemino-vagal reflex, may induce severe bradycardia and asystole. Fatal outcome has been described.[15 16]

These data from both observational reports and RCT suggest with different strengths of evidence, and hence different powers of causation and estimation of frequency, a clinically relevant relationship between propofol and bradycardia or asystole.

## Methods

A systematic search was made for any type of report (any or no study architecture) of bradycardic events during propofol anaesthesia. MEDLINE (KnowledgeServer) was searched (1984 to December 95), not restricted to the English language, with the terms *propofol, adverse effects* (sub-heading), *bradycardia, asystole* and *death,* and combinations of these words. Reference lists from published reports and review articles on propofol, and the authors' in-house bibliography on propofol were hand searched. Thirty-eight national centres participating in the WHO drug monitoring scheme were contacted by letter and asked for detailed information on spontaneous reports (yellow card scheme) on propofol and bradycardic events. The manufacturer of propofol was contacted to provide relevant data. Abstracts from scientific meetings, reports of propofol sedation in the ICU, reports of death not definitely related to bradycardic events (cardiovascular collapse without obvious relationship to bradycardia

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or asystole, for instance[17]) or of arrhythmias other than bradycardia[18] were not considered.

All types of reports were sought which supported a biological basis for propofol-induced bradycardia, reported absence or presence of bradycardic events with propofol anaesthesia or studied additional information on propofol-related bradycardia (prevention, therapy, risk factors, dose–response, pharmacological interactions).

Based on observational reports[9 19] there was a prior hypothesis that there is a potential continuum with propofol-induced bradycardia. This implies that bradycardia, which is usually perceived as minor harm, is actually potential major harm because of the possibility of its progressing to actual major harm, asystole and possibly to a disaster. Therefore, lowering of heart rate, OCR, and first or second degree AV blocks, as defined in the original reports, were considered as potential major harm. Asystole, cardiac arrest, absence of QRS complexes, electromechanical dissociation, and III degree AV block, as described in the original reports, were classified as major harm. Death after any bradycardic event was classified as disaster. Need for treatment (anticholinergics, catecholamines, external chest massage), concomitant symptoms (convulsion, for instance), and spontaneous resolution, duration, recurrence or grading of events (severe bradycardia, for instance) did not alter this classification.

Information on type of reports, patient characteristics, surgery, propofol regimen, concomitant drugs, anaesthetics in controls, definition, number and treatment of bradycardic events, and outcome was taken from each report. Dichotomous data on bradycardic complications in propofol and control groups were extracted from controlled trials.

The L'Abbé plot[20] of bradycardic event rates with propofol compared with bradycardic event rates with controls was used as a graphical means of exploring the risk of propofol and the homogeneity of the data set. A scatter predominantly lying between the line of equality and the propofol axis suggested an increased risk with propofol and homogeneity. Odds ratio (OR) estimates were calculated with 95% confidence intervals (CI) using a fixed effect model.[21] If any cell of a sample was zero, then 0.5 was added to all cell sizes for that sample.[22] A lower limit of the 95% CI of the OR $>1$ indicated a statistically significant increased risk with propofol. Number-needed-to-harm (NNH) and 95% CI were calculated in the same way as number-needed-to-treat.[23 24] Odds ratio and NNH were calculated separately for individual reports and by combining single propofol or control arms. It was assumed that propofol without nitrous oxide had the same risk of bradycardia as propofol with nitrous oxide; these arms were combined for analysis. The "rule of three"[25] was used in large series to estimate the implication of zero numerators. Calculations were performed using Excel v 5.0 on a Power Macintosh 7100/66.

## Results

Sixty-five published reports (1985–1995) were considered. Types of reports were randomized, controlled trials, controlled trials without randomization, a review of clinical studies, several case series and published case reports. Additional unpublished data came from 12 drug monitoring centres. Information from the manufacturer of propofol did not add to these data. No cohort or case-control study was found.

### BIOLOGICAL BASIS

Uncontrolled experiments in dogs with pharmacological autonomic denervation led to the conclusion that propofol may have a direct effect on sinus activity.[26] In an RCT in dogs, propofol decreased arterial pressure but failed to induce reflex tachycardia.[27] However, in rabbits[28] propofol increased heart rate, and in sheep[29] both heart rate and arterial pressure were increased with propofol. These findings were considered to be unexpected, contrasting with the response in human[28] and eventually were considered species-specific.[29]

Haemodynamic effects of propofol induction and maintenance were tested in several small clinical series[5 6 30–32] and one RCT.[33] Heart rate was stable or even decreased despite a significant decrease in arterial pressure.[6 30 33] Both baroreflex resetting[5 31] and a particular autonomic milieu predisposing to a parasympathetic response to noxious stimulation during propofol anaesthesia[32] were suggested as principal mechanisms of this relative bradycardia.

### BRADYCARDIC EVENTS WITH PROPOFOL IN CONTROLLED TRIALS

Seventeen relevant controlled trials were randomized.[34–50] In two further trials no method of randomization was mentioned.[51 52] Data from these 19 controlled clinical trials were pooled for analysis. In more than 1200 patients, propofol was compared with other regimens for induction or maintenance of anaesthesia, or both, and bradycardic events were reported as dichotomous outcomes (table 1). Children and adults, mainly ASA I or II, were studied in a variety of surgical settings. In five of 11 paediatric RCT the lower age limit was 6 months to 2 yr,[40 48 50 53 54] and in another three, age limits were not mentioned.[44 47 55] In one RCT,[37] five patients had heart disease and were classified as ASA III. Prophylactic anticholinergics were given in 11 studies. The event rate scatter suggested an increased risk of bradycardia with propofol and a homogeneous pattern in these trials (fig. 1). Across all controlled trials the risk with propofol, compared with other anaesthetics, was significantly increased; the combined NNH for one bradycardic episode was approximately 7 (table 1).

In an RCT a bradycardia ended in an asystole in a young woman undergoing a minor gynaecological procedure with propofol.[36] The patient was resuscitated successfully after external chest massage for 30 s and i.v. atropine. Her postoperative electrocardiogram showed a pre-excitation syndrome. The NNH point estimate for an asystole with propofol compared with another anaesthetic across all controlled studies was 660 (table 1).

*Table 1* Bradycardic events with propofol. Data from 17 randomized controlled trials and two controlled trials without randomization* (laps=laparoscopy, Paed=paediatric, AC=anticholinergics, n/′=beats per minute, HR=heart rate, N/A=not available, OCR=oculocardiac reflex, P=propofol, thio=thiopentone, metho=methohexitone)

| Ref | Surgery | Prophylactic AC | Other drugs | Bradycardic event (definition of bradycardia) | Comparison | Event rate with propofol | Event rate with control | Odds ratio (95% CI) | NNT (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| [34] | Adults different | No | Alfentanil | Bradycardia during induction (30/′) | P/alfentanil *vs* thio/suxamethonium | 1/31 | 0/33 | | |
| [35] | Micro ENT | Yes | Alfentanil, suxamethonium | Bradycardia during surgery (<50/′) | P *vs* etomidate | 1/15 | 0/15 | | |
| [36] | Minor gynaecology | No | None | Bradycardia during surgery (1 asystole) | P *vs* thio/halothane | 2/21 | 0/22 | | |
| [36] | Minor gynaecology | Yes | None | Bradycardia during surgery | P *vs* thio/halothane | 0/39 | 0/38 | | |
| [37] | Abdominal | No | Fentanyl, vecuronium | Bradycardia during surgery (<50/′ for >5 min) | P±$N_2O$ *vs* thio/isoflurane/$N_2O$ | 25/40 | 9/20 | | |
| [38] | Minor gynaecology | No | Fentanyl | Bradycardia during surgery (HR<50/′): atropine | P *vs* thiopental/isoflurane | 6/59 | 3/59 | | |
| [39] | Paed strabismus | Yes | Alfentanil, vecuronium | OCR during surgery (HR<15%) | P *vs* thio/halothane | 11/60 | 0/30 | | |
| [40] | Paed strabismus | Yes | Fentanyl, vecuronium | OCR during surgery (HR<20%) | P *vs* thio/halothane | 15/22 | 4/22 | | |
| [41] | ENT | Yes | Fentanyl, pancuronium | Bradycardia during surgery (definition N/A) | P *vs* thio/isoflurane | 0/25 | 3/25 | | |
| [42] | Adults different | No | Fentanyl, atracurium | Bradycardia during surgery (<45/′): atropine | P *vs* thio/isofurane | 1/25 | 0/25 | | |
| [43] | Gynaecology laps | Yes | Alfentanil, suxamethonium | Bradycardia during surgery (<50/′): 1x atropine (HR 37/′) | P *vs* P/isoflurane | 3/15 | 0/15 | | |
| [44] | Paed strabismus | Yes | Dextromoramide, vecuronium | OCR during surgery (HR<20%) | P *vs* P/enflurane | 9/21 | 3/21 | | |
| [45] | Gynaecology laps | No | Sufentanil, vecuronium | Bradycardia during surgery (definition N/A) | P *vs* thiamylal/enflurane | 8/30 | 9/30 | | |
| [46] | Orthopaedic | No | Fentanyl, d-tubocurarine | Complete heart block (HR 30/′) requiring atropine at induction | P *vs* desflurane | 0/23 | 1/46 | | |
| [47] | Paed ENT | Yes | Suxamethonium | Bradycardia (definition N/A) or junctional rhythm at induction | P *vs* barbiturates | 14/75 | 2/48 | | |
| [48] | Paed strabismus | Yes | Alfentanil, vecuronium | OCR during surgery (HR<20%) | P *vs* thio/isoflurane | 10/20 | 3/20 | | |
| [49] | Laryngoscopy | Yes | Alfentanil, suxamethonium | Bradycardia (N/A) during surgery treated with atropine | P *vs* midazolam/thio and metho | 1/20 | 0/20 | | |
| [50] | Paed strabismus | Yes | Morphine, vecuronium | OCR during surgery (HR<15%) | P *vs* halothane | 41/90 | 10/30 | | |
| *[51] | Thoracoabdominal | No | Fentanyl, vecuronium | Bradycardia during surgery (38/′–46/′) | P *vs* thio/halothane | 5/20 | 0/20 | | |
| *[52] | Aortic | No | Fentanyl, vecuronium | Bradycardia+hypotension +ST depression | P *vs* etomidate | 1/9 | 0/9 | | |
| Bradycardic events: combined studies | | | | | | 154/660 | 47/548 | 2.5 (1.8–3.6) | 6.8 (5.3–9.3) |
| Asystole: combined studies | | | | | | 1/660 | 0/548 | 2.3 (0.1–37) | 660 |
| Sensitivity analysis | | | | | | | | | |
| Bradycardic events combined: only OCR | | | | | | 86/213 | 20/123 | 3.4 (2–5.6) | 4.1 (3–6.7) |
| Bradycardic events combined: not OCR | | | | | | 68/447 | 27/425 | 2.3 (1.5–3.4) | 11.3 (7.7–21) |

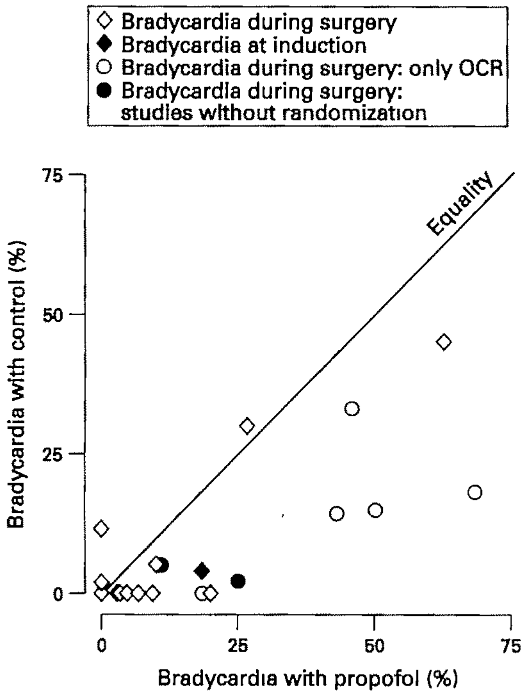

*Figure 1* Propofol and bradycardic events. Each symbol represents one study. Numbers indicate percentages of patients with a bradycardic event with propofol or a non-propofol anaesthetic (control). Data from 17 randomized, controlled trials and two controlled trials without randomization.

In five RCT with more than 330 children undergoing strabismus surgery the average incidence of an OCR in controls was 16.2%.[39 40 44 48 50] In these studies the combined NNH for an OCR with propofol was 4, despite prophylactic anticholinergics (table 1). In all other controlled trials (12 RCT and two controlled trials without randomization) the average incidence for bradycardia in controls was 6.4%, and the NNH to produce a bradycardia with propofol was approximately 11 (table 1).

## BRADYCARDIC EVENTS WITH PROPOFOL IN CASE SERIES

In a small series, one of 30 patients needed atropine to treat bradycardia.[56] An early review of the safety and tolerance of propofol based on 27 separate studies with 1459 patients receiving propofol reported one cardiac arrest.[57] A cardiac conduction defect was thought to be a contributory factor to this major complication.[57] No bradycardic events were reported in a post-launch trial involving 879 patients receiving propofol.[58] In more than 2600 children and adults undergoing a standard propofol anaesthetic, two III degree AV blocks and one bradycardia progressing into an asystole were described in three healthy adults.[59]

The results of a propofol phase IV study were described in two separate analyses.[60 61] One analysis concentrated on any type of adverse event during propofol anaesthesia, as reported by anaesthetists and nurses.[60] Without definitions, this article documented intraoperative bradycardia in 102 (0.4%), severe bradycardia in four and cardiac arrest in two of 25 981 patients, respectively.[60] The second analysis of the same data concentrated specifically on the haemodynamic effects of propofol anaesthesia and reported a 2% incidence of bradycardia (heart rate lower than 50 beat $\text{min}^{-1}$) at induction and an additional 2.8% during maintenance.[61] In a *post hoc* analysis, bradycardia was significantly associated with beta-blockers, but not with anticholinergics, opioids, neuromuscular blocking agents or heart disease.[61] Hug and colleagues concluded that even in the hands of inexperienced anaesthetists propofol had a low incidence of untoward haemodynamic changes and that these changes were predictable.[61]

## BRADYCARDIC EVENTS WITH PROPOFOL IN PUBLISHED CASE REPORTS

Seventeen published case reports from 10 countries described, in 25 adults, 13 bradycardias, three heart blocks, 13 asystoles, one electromechanical dissociation and one death.[7–9 19 62–74] Seven bradycardias progressed to asystole. In an elderly patient with atrial flutter, electromechanical dissociation without preceding bradycardia had a fatal outcome; post-mortem examination excluded acute myocardial ischaemia.[74] Case reports were published between 1987 and 1994 without any chronological clustering.

## BRADYCARDIC EVENTS WITH PROPOFOL IN SPONTANEOUS REPORTS TO DRUG MONITORING CENTRES

Twelve of 38 national drug monitoring centres responded to our inquiry. In three countries (Croatia, New Zealand, Thailand) no bradycardic events were reported. The other nine countries reported 95 bradycardias, 65 asystoles and 23 bradycardia-related deaths during propofol anaesthesia: Australia (six reports), Belgium (six), Canada (four), Denmark (five), Eire (11), Norway (five), Sweden (two), Switzerland (one) and UK (147). Twenty-five bradycardias progressed to asystole; nine of these were fatal. Death was documented in another 14 patients after asystole.

## ADDITIONAL DATA

In RCT in children, the reduction in heart rate with propofol was more pronounced when alfentanil was also given,[55] was not dose-dependent[54 75] and was more pronounced in children less than 2 yr of age than in older children[53] but was not different between the ages of 3 and 15 yr.[75] One study without randomization reported a lower incidence of OCR with a higher propofol dosage regimen.[76]

In adults, anticholinergic agents prevented propofol-induced bradycardia but not hypotension.[77–79] Established bradycardia was unresponsive to increasing doses of i.v. atropine.[80] Bradycardia was potentiated by fentanyl,[81 82] but was not increased when lignocaine was given to prevent propofol pain at injection.[83] A tendency to slower heart rates was seen in older patients (65–80 yr) undergoing propofol anaesthesia compared with younger patients (25–40 yr).[84] A dose–response was seen for hypotension but not for bradycardia in elderly patients.[85]

*Table 2* Propofol and bradycardic events. Absolute risk (AR) and ratio in 19 controlled trials (17 RCT, two trials without randomization*), four case series and one review of 27 studies

| Report | A: Potential major harm AR of bradycardia with propofol (per 100 patients) | B: Major harm AR of asystole with propofol (per 10 000 patients) | C: Disaster AR of bradycardia-related death (per 100 000 patients) | A:B Ratio | Ref. |
|---|---|---|---|---|---|
| Controlled trials: without OCR | 15.2 (68/447) | *15.2 (1/660)* | *N/A* | N/A | [34–38,41–43, 45–47, 49],*[51],*[52] |
| Controlled trials: only OCR | 40.4 (86/213) | | | N/A | [39,40,44,48,50] |
| *Controlled trials combined* | *23.3 (154/660)* | *15.2 (1/660)* | *N/A* | *154:1* | |
| Series (phase IV) | 4.8 (1178/24 548) | 0.8 (2/25 981) | 0 (0/25 981) ("rule of 3": at most 12) | 623:1 | [61,60] |
| Series (post-launch) | N/A | 0 (0/860) ("rule of 3": at most 35) | N/A | N/A | [58] |
| Series (ophthalmologic surgery) | N/A | 11.5 (3/2606) | N/A | N/A | [59] |
| Small series | 3.3 (1/30) | 0 (0/30) | N/A | 1:0 | [56] |
| Review (27 studies) | N/A | 6.9 (1/1459) | N/A | N/A | [57] |
| *Series combined* | 4.8 (1179/24 578) | *With phase IV: 1.9 (6/30 936)*<br>*Without phase IV: 8.1 (4/4955)* | N/A | *240:1* | |

## ESTIMATION: ABSOLUTE RISK OF BRADYCARDIC EVENTS WITH PROPOFOL

The likelihood of bradycardic events with propofol depended on the type of report (table 2). In 19 controlled trials the average incidence of bradycardia with propofol was 23.3% in 660 patients (15.2% when OCR was excluded). In case series the incidence of bradycardia with propofol was 4.8% (1179 bradycardic events in 24 578 patients).

In controlled trials one of 660 propofol patients developed an asystole, corresponding to an incidence of 15 asystoles in 10 000 patients (table 2). In uncontrolled series, six asystoles were described in 30 936 patients receiving propofol, corresponding to an incidence of 1.9 asystoles in 10 000 treated patients (8.1 in 10 000 when the phase IV study was excluded).

The post-launch study did not report asystole and the phase IV trial did not report death; one can then be 95% confident that an asystole with propofol anaesthesia does not happen more often than 35 times in 10 000 patients, and that not more than 12 deaths caused by bradycardia happen in 100 000 propofol anaesthetics.[25]

## ESTIMATION: RATIOS BETWEEN ABSOLUTE RISKS OF DIFFERENT LEVELS OF HARM

In controlled trials one of 154 bradycardic episodes led to an asystole (table 2). Across all case series, including the review of 27 studies, an average of 240 bradycardias led to one asystole. In the phase IV trial alone, 623 bradycardias led to one asystole. Death was not reported in controlled studies or case series, therefore calculation of a ratio between major harm and disaster is not possible.

In observational reports (case reports and spontaneous reports to drug monitoring centres) approximately four bradycardias led to one asystole and one-third of asystoles were fatal (table 3). Asystole after propofol-induced bradycardia was 43 times more likely to be reported in observational reports than in controlled trials.

## QUALITATIVE ANALYSIS OF PUBLISHED REPORTS

Bradycardic complications occurred after induction, during or at the end of propofol anaesthesia. An abrupt, unpredictable decrease, or a progressive slowing of the heart rate, and sudden cardiac arrests were reported. Associated complications involved

*Table 3* Propofol and bradycardic events: ratios in observations (published case reports and spontaneous reports to drug monitoring centres)

| Report | A: Potential major harm Bradycardia | B: Major harm Asystole | C: Disaster Death | A:B Ratio | B:C Ratio | Ref |
|---|---|---|---|---|---|---|
| Case reports ($n=23$) | A(1)=16 | B(1)=7 | C(1)=0 | A(1):B(1)=2.3 | B(1):C(1)=0 | [9],[19],[63],[72-74] |
| | | B(2)=7 | C(2)=1 | n/a | B(2):C(2)=7 | [74] |
| Spontaneous reports ($n=187$) | A(2)=95 | B(3)=25 | C(3)=9 | A(2):B(3)=3.8 | B(3):C(3)=2.8 | |
| | | B(4)=40 | C(4)=14 | n/a | B(4):C(4)=2.9 | |
| *Combined A:B* | A(1+2)=111 | B(1+3)=32 | | *A(1+2):B(1+3)=3.5* | | |
| *Combined B:C* | | B(1+2+3+4)=79 | C(1+2+3+4)=24 | | *B(1+2+3+4):C(1+2+3+4)=3.3* | |

tonic–clonic movements,[64] arrhythmia of unknown type,[36] junctional rhythm,[63 64] supraventricular bradycardia,[65] recurrence of asystole,[67 70] and intermittent episodes of heart block.[70]

Treatment of bradycardic events consisted in most cases of i.v. administration of anticholinergics, but also catecholamines,[7 51 52 59] precordial chest thump[65] and external cardiac massage.[36 59 63 72] Resistance to both i.v. atropine[7 51 52 59 65] and isoprenaline[7] was reported. In several reports heart rate normalization occurred after stopping the propofol infusion.[7 51 52 66] Several bradycardic episodes resolved spontaneously. The longest duration of asystole in surviving patients was 45 s.[64]

Several factors, alone or in combination, were coincident with bradycardic complications during propofol anaesthesia and were therefore suspected in the original reports to be jointly responsible for the negative outcome: surgical stimulation,[9 36] lack of surgical stimulation,[63 67] extradural anaesthesia,[51] previous syncope,[7 64 67] preoperative conduction abnormalities,[57 71] fentanyl,[8 63 65] suxamethonium,[35 62 65] atracurium,[8] beta-blocker,[61 70] ornipressin,[8] neostigmine,[70] any factors or drugs potentiating vagal stimulation,[19 68–70 72 73] absence of vagal stimulation,[63] too light anaesthesia,[76] insufficient prophylactic dose of atropine[48 50] and an individual susceptibility to propofol.[63 65] Most authors concluded that a prophylactic anticholinergic may be indicated in the presence of any risk factor if propofol is to be used.

## Discussion

We have described a new approach to adverse event reporting. The focus was on one particular complication with one particular drug.

The three main results of this study are of both methodological and clinical importance: first, a systematic approach to adverse event reporting, taking into account all types of reports with data of different strengths of evidence and both quantitative and qualitative analysis of the extracted data is possible; second, the additional risk of bradycardic events with propofol anaesthesia is finite, compared with other anaesthetic regimens; third, bradycardia with propofol is potential major harm.

Information on propofol anaesthesia and bradycardic events came from different sources. First, the biological basis for propofol-induced bradycardia was supported by several experimental animal and human studies. A plausible physiopathological mechanism explaining the occurrence of an adverse event during or after exposure to the treatment in question supports a causal association between adverse event and treatment.

Second, combined analysis of controlled trials showed a statistically significant difference between propofol and other anaesthetics. In non-ophthalmological settings the additional risk of bradycardia with propofol was approximately 9% (number-needed-to-harm 11.3) compared with other anaesthetics. In these studies the average risk of a bradycardic event in controls was less than 7%. In paediatric strabismus surgery where all children received prophylactic anticholinergics, the ability of propofol to produce a bradycardia caused by the OCR was even more pronounced; one of four children treated with propofol will have a bradycardic episode which would not have happened with another anaesthetic. In these latter studies the average incidence of bradycardia in controls was twice as high as in non-ophthalmological settings. This sensitivity analysis was another example of the clinically important relationship between the risk of an outcome without intervention and the number of patients needed to be treated with the intervention in order to produce such an outcome.[86] Although there is no way of assessing the risk for an individual patient, these results may influence clinicians' choice of interventions for particular groups of patients. These data strongly suggest that propofol is very likely to increase the incidence of bradycardic events compared with other anaesthetic regimens in any clinical setting with an increased risk of bradycardia.[87]

Third, the post-marketing surveillance study of propofol, although including almost 26 000 patients, did not contribute importantly to this analysis. This large but uncontrolled study was praised as having the unique advantage of systematically collected information, and was therefore presumed to reflect adequately the incidence of clinically significant adverse events.[60] However, the two published analyses of this trial did not agree. While a very low incidence of bradycardia (0.4%) but two cardiac arrests were reported in one,[60] the incidence of bradycardia was 10 times higher but no cardiac arrests reported in the other.[61] These differences challenge the reliability of these reports. Compared with controlled studies bradycardia was 3–4 times and asystole 19 times less likely to be reported in this case series, and four times as many bradycardias were necessary to produce one asystole (table 2). Only after combination with data from other series did absolute risk and ratios come closer to data from controlled trials. Drawbacks of phase IV studies have been pointed out previously.[88]

Fourth, in this analysis we used both published case reports and spontaneous reports to drug monitoring centres not only for description of a new or very rare adverse event [89] but to estimate the frequency of disaster. The majority of uncontrolled observations on adverse events are examples of the most dramatic though rare clinical scenarios imaginable. Indeed, published case reports are expected to draw attention to important clinical situations, unusual clinical phenomena and complications.[90] Therefore, in such reports ratios between different levels of harm are obvious overestimations of the clinical reality. But these reports are often the only source, which makes it possible to establish a ratio between major harm and disaster. Observations enabled a link between all three levels of harm to be made.

There is strong evidence that bradycardia is more likely to happen with propofol than with other anaesthetics. The question then is how serious is propofol-induced bradycardia? One response is to interpret it as minor harm, trivial and of no clinical importance. Such a response may not be correct. The prior hypothesis that propofol-induced bradycardic events may be an example of a continuum was supported consistently by data from all types of study. This implies that bradycardia during propofol anaesthesia cannot be discounted as minor harm but should be classified as potential major harm. Therefore, major harm and consequential disaster cannot be ignored and their likelihood has to be estimated. There is strong evidence from controlled trials that the incidence of asystole may be of the order of 15 in 10 000 patients receiving propofol anaesthesia. Uncontrolled series gave estimates with less strong evidence; the numbers were 0.8, 6.9, 11.5 and at most 35 asystoles per 10 000 patients, respectively. These numbers are difficult to interpret because of the lack of a comparator. The number-needed-to-harm calculation is more powerful because it enables comparison of the treatment in question with a control, in this case with another anaesthetic. Based on controlled studies, one of 660 patients undergoing propofol anaesthesia may have an asystole caused by propofol, who would not have had such a major complication in the same clinical setting with a different anaesthetic.

The next question is, what is the likelihood that propofol-induced asystole leads to death? Asystole was not always fatal. Several spontaneous restorations of sinus rhythm were described, but on some occasions treatment included catecholamines and external chest massage. Propofol-related bradycardia and asystole may indeed be of minor clinical importance if occurring in healthy subjects and adequately managed.

Different potential quantitative scenarios may be described. Death occurred only in observational reports. Ratios suggested that in the worst situation one-third of propofol-induced bradycardias may lead to an asystole, and that one-third of all asystoles may be fatal. In a worst-possible scenario with the most disastrous constellation of risk factors, these ratios from observational reports, together with a 15% absolute risk for bradycardia from controlled trials (strabismus surgery excluded), would translate into an incidence of 128 deaths in 10 000 propofol anaesthetics. However, the ratio between bradycardia and asystole in observational reports seemed to be a 43-fold overestimation compared with controlled trials. The most likely true ratio between propofol-induced asystole and death may then equal the observation-based ratio times this overestimation factor (i.e. 3.3 times 43 or one death after 112 asystoles). This corrected asystole–death ratio together with the absolute risk for asystole in controlled trials (one in 660 propofol anaesthetics) translates into 1.4 bradycardia-related deaths per 100 000 propofol anaesthetics. This number is in agreement with the rule-of-three estimation from the phase IV trial (at most 12 deaths in 100 000). This number is also in agreement with the estimate that one death attributable to any type of anaesthetic occurred in 20 000 operations in New South Wales between 1984 and 1990.[91] Death caused by bradycardic complications during propofol anaesthesia would then constitute approximately one-fifth of all anaesthesia-related deaths.

What clinical lessons can be drawn from this analysis? According to the manufacturer's data sheet, propofol should be given by those trained in anaesthesia or, where appropriate, doctors trained in the care of patients in intensive care. Severe bradycardia and asystole as possible complications of propofol are mentioned and the manufacturer suggests the prophylactic use of anticholinergics in patients at particular risk for bradycardia, and advises against the use of propofol for induction of anaesthesia in children less than 3 yr of age. These statements are supported by this study. Some comments may, however, be appropriate.

First, despite prophylactic anticholinergics the risk of bradycardia with propofol may still be considerable.[7–9, 35, 39, 40, 43, 44, 47, 48, 50, 51] Several reports suggested an inadequate response of propofol-induced bradycardia to atropine.[7, 51, 52, 59, 65, 80] Especially in children, prevention and treatment of bradycardia with atropine is controversial.[92] In this context, the suggestion that the prophylactic dose of atropine should be increased seems to be inappropriate.[48, 50]

Second, a stable heart rate accompanied by a decrease in cardiac output and systemic vascular resistance may result in inadequate peripheral perfusion pressure and oxygen delivery.[27] In young children cardiac output is more rate-dependent than in adults because of a limited ability to increase myocardial contractility.[93] The frequency of bradycardia during anaesthesia in children increases with both decreasing age and poorer ASA physical status.[94] There is evidence that propofol decreases heart rate more in children less than 2 yr of age compared with older children.[53] The pragmatic question is then, what happens to a young child who is very ill and who receives a long-term propofol infusion? Five of seven seriously ill ICU children who developed refractory bradyarrhythmia after prolonged propofol sedation were between 4 weeks and less than 3 yr old; in four the outcome was fatal.[10–12]

Third, physicians' perception of frequency and severity of harm together with their skills to treat major complications and to prevent a disaster may have an important impact on judging the risk:benefit of treatments. For instance, bradycardia caused by OCR has been recognized as an important intraoperative complication of strabismus surgery.[16, 95–96] However, two of seven published RCT comparing propofol with another anaesthetic in paediatric strabismus surgery did not report any information on the presence or absence of the OCR.[97, 98] The other five studies reported a much higher incidence of the OCR with propofol than with other anaesthetics despite prophylactic anticholinergics, but none questioned the indication for propofol in this setting.[39, 40, 44, 48, 50] Also, estimate of the asystole–death ratio of propofol may be perceived as being extremely low and therefore of no importance. However, this ratio describes only deaths caused by bradycardia-related complications during propofol anaesthesia. Inclusion of other possibly propofol-related deaths, such as cardiovascular collapse,[17] would have given a less favourable estimate. Most bradycardias and asystoles seem to have been adequately managed by anaesthetists, including resuscitation measurements such as i.v. catecholamines and external chest compression. The same quantity and severity of potential major and major harm in hands of physicians not used to such resuscitation techniques would probably have given different results.

Finally, the first contraindication to any drug is lack of indication.[92] Propofol anaesthesia is by no means a treatment without alternatives. It would therefore be helpful to identify both the subgroups most likely to profit from the beneficial characteristics of propofol and the subgroups at particular risk of complications. For instance, faster recovery and decreased incidence of postoperative nausea and vomiting after propofol anaesthesia are unlikely to be of clinical relevance in every setting.[99–101] Results from the sensitivity analysis, together with data from different reports, suggest that the indications for propofol should at least be questioned in the presence of conduction abnormalities,[36,57,71,74] heart rate lowering medications such as beta-blockers,[61,70] procedures with an increased risk of bradycardia,[87] including squint repair,[14] and laparoscopies,[32,43,69,102] and in very sick, old or young patients.[10–12,17,53,74,84,103]

This article has described an approach to adverse events which showed a biological progression. The example used was propofol bradycardia, asystole and death. It would be misleading to use this hazard out of context. Clearly there are many other hazards in anaesthesia which need to be considered; not all are as well documented. This model may be useful to allow us to be more precise about the other hazards.

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# Phantom pain and sensation among British veteran amputees

S. W. WARTAN, W. HAMANN, J. R. WEDLEY AND I. MCCOLL

## Summary

Using a mail-delivered questionnaire, we surveyed 590 veteran amputees concerning phantom pain, phantom sensation and stump pain. They were selected randomly from a population of 2974 veterans with long-standing limb amputation(s) using a computer random number generator. Eighty-nine percent responded and of these, 55% reported phantom limb pain and 56% stump pain. There was a strong correlation between phantom pain and phantom sensation. The intensity of phantom sensation was a significant predictor for the time course of phantom pain. In only 3% of phantom limb pain sufferers did the condition become worse. One hundred and forty-nine amputees reporting phantom pain discussed their pain with their family doctors; 49 were told that there was no treatment available. Transcutaneous electric nerve stimulation, analgesics and non-steroidal anti-inflammatory drugs were satisfactory methods for controlling phantom limb pain. (*Br. J. Anaesth.* 1997; **78**: 652–659).

**Key words**
Pain, phantom limb. Analgesia, audit.

Knowledge of the persistence of sensation in a limb which has been removed must be as old as survival from amputation. Nevertheless, it was not until 1551 that the French military surgeon Ambroise Pare recorded the condition clearly when discussing amputations.[1] In 1871 Silas Weir Mitchell published his article "phantom limbs" and gave us this term which has had universal usage.[2] The phantom limb can be either painless (termed phantom limb sensation) or painful (phantom limb pain).

Virtually all amputees have various types of persistent phantom sensations.[3] The relation of these sensations to phantom pain is still not clear. The frequency of chronic phantom limb pain has been a matter of debate. It ranges between 1% and 98% in various studies.[4–8] One explanation for an apparent low incidence is probably the poor therapeutic consequences of treatment.

The aim of this investigation was to establish the incidence and time course of phantom limb and stump pain in long-standing amputees, to determine if there is a link between phantom sensation and phantom pain, and to examine the choice and effectiveness of treatment.

## Patients and methods

### POPULATION SURVEYED

The British Limbless Ex-Servicemen's Association (BLESMA) supplied a list of all 2974 members. Members of BLESMA are mainly old veterans with limb amputation(s) from World War II, the Falklands war and a few survivors from World War I. We selected randomly 590 members (approximately a one in five sample) to receive the questionnaire using a computer random number generator. All individuals selected were male amputees. A pilot study of 30 questionnaires was carried out before the main study to assess the rate of response and test the clarity of the questionnaire. The response for the pilot study was 85%.

### THE QUESTIONNAIRE

The survey instrument shown in figure 1 consisted of four pages which was a modification of the questionnaire used by Sherman, Sherman and Parker.[4] Each questionnaire was sent with a stamped addressed envelope and a personally addressed covering letter briefly defining phantom pain, phantom sensation and stump pain, and this was repeated at the beginning of relevant sections in the questionnaire. The covering letter included a clear request for all recipients to respond regardless of the presence or absence of phantom or stump pain.

Explanation of the method to rate pain was given at the beginning of the questionnaire. The same method was used to rate the uncomfortable phantom sensation. Questions required yes/no or do not know, rating scale or short answers. The questionnaire consisted of the following sections.

### *Patient characteristics and amputation history*

Questions requested information on age, sex, reason for amputation, number of years since amputation, site of amputation, presence or absence of pain in the limb before amputation and use of prostheses.

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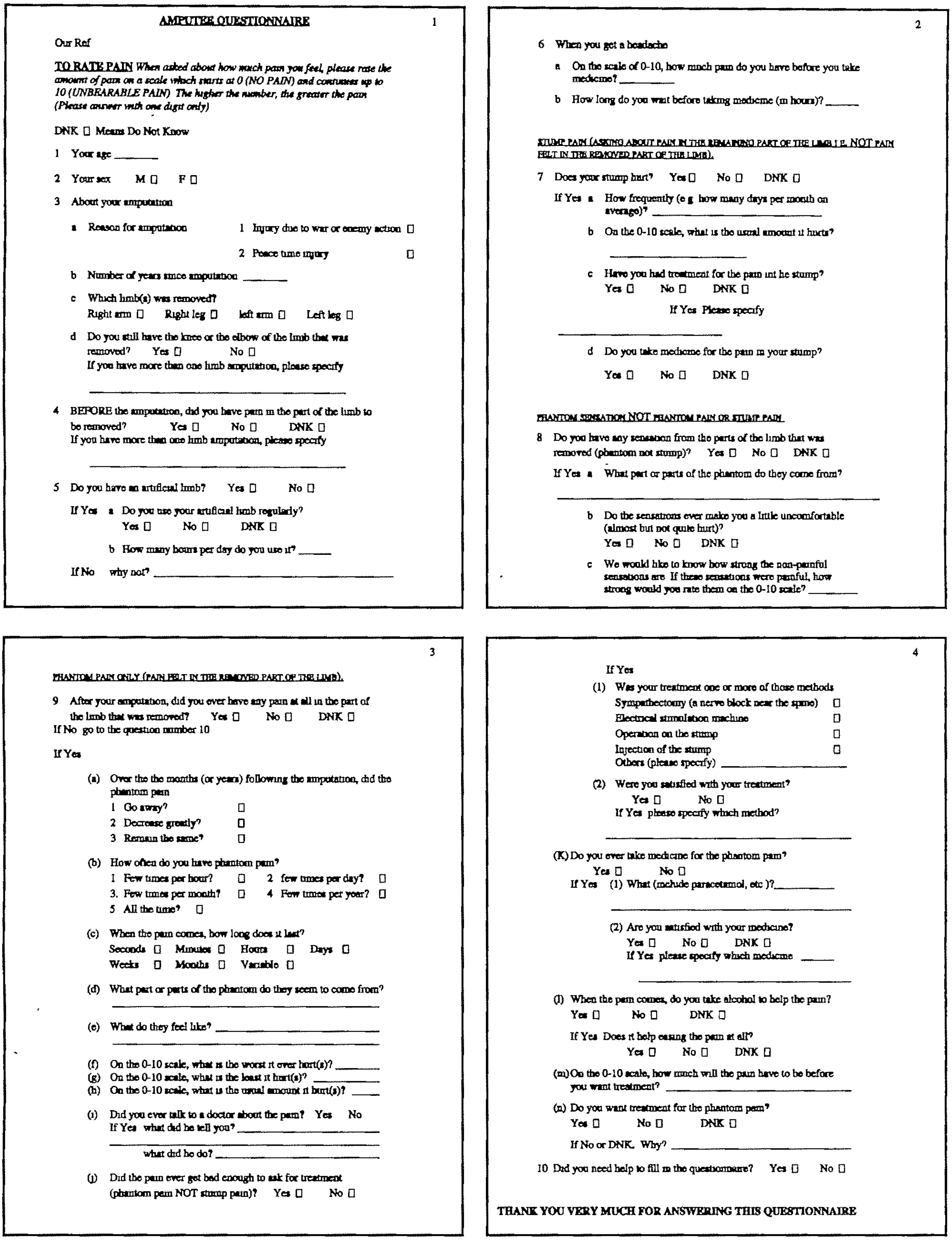

**AMPUTEE QUESTIONNAIRE** 1

Our Ref

TO RATE PAIN *When asked about how much pain you feel, please rate the amount of pain on a scale which starts at 0 (NO PAIN) and continues up to 10 (UNBEARABLE PAIN) The higher the number, the greater the pain (Please answer with one digit only)*

DNK ☐ Means Do Not Know

1 Your age ________

2 Your sex M ☐ F ☐

3 About your amputation

a Reason for amputation 1 Injury due to war or enemy action ☐
2 Peace time injury ☐

b Number of years since amputation ________

c Which limb(s) was removed?
Right arm ☐ Right leg ☐ left arm ☐ Left leg ☐

d Do you still have the knee or the elbow of the limb that was removed? Yes ☐ No ☐
If you have more than one limb amputation, please specify
________________________________

4 BEFORE the amputation, did you have pain in the part of the limb to be removed? Yes ☐ No ☐ DNK ☐
If you have more than one limb amputation, please specify
________________________________

5 Do you have an artificial limb? Yes ☐ No ☐

If Yes a Do you use your artificial limb regularly?
Yes ☐ No ☐ DNK ☐

b How many hours per day do you use it? ______

If No why not? ________________________________

2

6 When you get a headache

a On the scale of 0-10, how much pain do you have before you take medicine? __________

b How long do you wait before taking medicine (in hours)? _______

STUMP PAIN (ASKING ABOUT PAIN IN THE REMAINING PART OF THE LIMB I E. NOT PAIN FELT IN THE REMOVED PART OF THE LIMB).

7 Does your stump hurt? Yes ☐ No ☐ DNK ☐

If Yes a How frequently (e g how many days per month on average)? ________________

b On the 0-10 scale, what is the usual amount it hurts?
________________

c Have you had treatment for the pain int he stump?
Yes ☐ No ☐ DNK ☐
If Yes Please specify
________________

d Do you take medicine for the pain in your stump?
Yes ☐ No ☐ DNK ☐

PHANTOM SENSATION NOT PHANTOM PAIN OR STUMP PAIN

8 Do you have any sensation from the parts of the limb that was removed (phantom not stump)? Yes ☐ No ☐ DNK ☐

If Yes a What part or parts of the phantom do they come from?
________________________________

b Do the sensations ever make you a little uncomfortable (almost but not quite hurt)?
Yes ☐ No ☐ DNK ☐

c We would like to know how strong the non-painful sensations are If these sensations were painful, how strong would you rate them on the 0-10 scale? ________

3

PHANTOM PAIN ONLY (PAIN FELT IN THE REMOVED PART OF THE LIMB).

9 After your amputation, did you ever have any pain at all in the part of the limb that was removed? Yes ☐ No ☐ DNK ☐
If No go to the question number 10

If Yes

(a) Over the the months (or years) following the amputation, did the phantom pain
1 Go away? ☐
2 Decrease greatly? ☐
3 Remain the same? ☐

(b) How often do you have phantom pain?
1 Few times per hour? ☐ 2 few times per day? ☐
3. Few times per month? ☐ 4 Few times per year? ☐
5 All the time? ☐

(c) When the pain comes, how long does it last?
Seconds ☐ Minutes ☐ Hours ☐ Days ☐
Weeks ☐ Months ☐ Variable ☐

(d) What part or parts of the phantom do they seem to come from?
________________________________

(e) What do they feel like? ________________
________________________________

(f) On the 0-10 scale, what is the worst it ever hurt(s)? ________
(g) On the 0-10 scale, what is the least it hurt(s)? ________
(h) On the 0-10 scale, what is the usual amount it hurt(s)? _____

(i) Did you ever talk to a doctor about the pain? Yes No
If Yes what did he tell you? ________________
________________________________
what did he do? ________________

(j) Did the pain ever get bad enough to ask for treatment (phantom pain NOT stump pain)? Yes ☐ No ☐

4

If Yes

(1) Was your treatment one or more of those methods
Sympathectomy (a nerve block near the spine) ☐
Electrical stimulation machine ☐
Operation on the stump ☐
Injection of the stump ☐
Others (please specify) ________________

(2) Were you satisfied with your treatment?
Yes ☐ No ☐
If Yes please specify which method?
________________________________

(K) Do you ever take medicine for the phantom pain?
Yes ☐ No ☐
If Yes (1) What (include paracetamol, etc )?__________
________________________________

(2) Are you satisfied with your medicine?
Yes ☐ No ☐ DNK ☐
If Yes please specify which medicine ______
________________________________

(l) When the pain comes, do you take alcohol to help the pain?
Yes ☐ No ☐ DNK ☐

If Yes Does it help easing the pain at all?
Yes ☐ No ☐ DNK ☐

(m) On the 0-10 scale, how much will the pain have to be before you want treatment? ________________

(n) Do you want treatment for the phantom pain?
Yes ☐ No ☐ DNK ☐

If No or DNK. Why? ________________

10 Did you need help to fill in the questionnaire? Yes ☐ No ☐

**THANK YOU VERY MUCH FOR ANSWERING THIS QUESTIONNAIRE**

*Figure 1* The four-page amputee questionnaire.

## *Pain sensitivity and attitude towards use of medical treatment for pain not related to the amputation*

We wished to ascertain if respondents who request treatment for their phantom pain were different in their sensitivity to pain or in their attitude towards medicine than respondents not requesting treatment. Questions on the intensity and duration of headache before taking medicine were asked in this section.

## *Stump pain*

Questions asked if the stump hurt, the frequency and intensity of pain, methods of treatment and use of medication.

### *Phantom sensation*

This section was intended to differentiate between the benign phantom sensation and the uncomfortable sensation. Information on location and intensity of phantom sensation when uncomfortable were asked to relate them to the painful phantom.

### *Phantom pain*

This was the largest section in the questionnaire. Questions asked about the presence of phantom pain, time course, frequency and duration of attacks, location and description, intensity of pain and if respondents with phantom pain ever asked their doctors about the pain and the response to their question. A series of questions asked about the different methods of treatment offered when the respondent requested treatment for the phantom pain and satisfaction with treatment, including self-medication and alcohol. A question to gauge the intensity of phantom pain before requesting treatment was asked to relate to similar questions regarding headache. Reasons for not requesting treatment for phantom pain were explored by another question.

### *Help*

As most members of BLESMA are senior citizens, a question ascertained the reliability of the returned completed questionnaire by asking if the questionnaire was answered by the individual himself.

### STATISTICAL ANALYSIS

We used the statistical software, SPSS for Windows version 6.1, for analysis of our data. Student's $t$ test was used for comparison of the means of two groups of data measured on an interval scale, for example age. The Mann–Whitney $U$ test was used for comparison of the means of two groups of data measured on an ordinal scale, for example pain measurement scale. Chi-square tests were used for comparison of non-numeric data and frequency of occurrence; these tests indicate if a series of events occurred with equal frequency among several groups. Differences were considered significant if the probability ($P$) was equal to or less than 0.01. Statistical significance was used only as a guide towards determining the clinical significance of different patterns.

## Results

### RESPONSE RATE

Of the 590 questionnaires sent out, 10 were returned by the postal service as not delivered and 22 were returned by the addressee's relatives as members were either mentally not fit to answer or were deceased. Only 32 failed to respond. The total number of evaluable questionnaires returned was thus 526 (89%). This was achieved by sending two waves of questionnaires, 8 weeks apart. The second wave was sent only to non-responders, which increased the response rate from 81% to 89%. Forty-five respondents accompanied their completed questionnaires with letters containing further information and notes of thanks for our interest.

### RELIABILITY OF THE DATA

Only 10.7% of respondents needed help to complete the questionnaire. Most of the respondents who needed assistance accompanied their answers by comments explaining the reason, which were mainly because of instability of the hand, for example parkinsonism.

### SAMPLE CHARACTERISTICS

All respondents' amputations were of traumatic origin. Eighty-nine percent were sustained during active service. Median age and number of years since amputation were 73 and 50 yr, respectively. Approximately 87% of respondents had a lost limb(s) for the past 30–50 yr, few for even longer. Almost 50% of respondents had below knee amputation (table 1).

### PHANTOM PAIN AND STUMP PAIN FREQUENCY AND CHARACTERISTICS

Three-hundred and twenty-six respondents reported unambiguously the feeling of phantom pain, while 18 respondents were either not sure or were confusing phantom pain and stump pain despite the advice in our covering letter and questionnaire to clarify the difference. These 18 respondents were considered as not reporting phantom pain. Therefore, the frequency of phantom pain in 590 veterans surveyed was 55.2%, assuming the "best possibility" that all non-respondents had no phantom pain. Three-hundred and thirty-four respondents reported stump pain (56.6%), of whom 220 reported phantom pain and stump pain. Duration of stump pain was reported as a mean of 13 (SEM 0.65) days per month. Respondents were asked to rate the intensity of their pain on a 0–10 scale (0=no pain, 10=unbearable pain). Mean intensities of stump pain and phantom pain were 6.2 and 5.6, respectively ($P$=0.002). On the same scale the means of their least and worst phantom pain were 3.6 (SEM 0.15) and 7.8 (0.15), respectively. There were no significant differences in relation to stump pain intensity between respondents reporting phantom pain and respondents not reporting phantom pain (mean 6.1 and 6.5, respectively) ($P$=0.14).

*Table 1* Site of amputation. Note some respondents had more than one limb amputation

| Site | No. of respondents (%) |
|---|---|
| Above elbow | 10.3 |
| Below elbow | 8.5 |
| Above knee | 41.8 |
| Below knee | 47.7 |

*Table 2* Phantom pain description. Note some respondents reported more than one description

| Description | No. (%) |
|---|---|
| Stabbing | 24.3 |
| Pins and needles | 20.5 |
| Cannot describe the pain | 16.0 |
| Shooting (electric shock) | 12.8 |
| Cramping | 12.8 |
| Crushing | 10.1 |
| Burning | 9.4 |
| Abnormal position | 4.5 |
| Leg jumps | 4.5 |

Phantom pain disappeared completely in 52 (16%) respondents reporting phantom pain and decreased substantially in another 121 (37%), while it remained the same in 144 (44%) and even increased in nine (3%) respondents reporting phantom pain. One hundred and thirty-three (41%) respondents reporting phantom pain had a few attacks of pain every month, 81 (25%) fewer attacks per year, 53 (16%) had bouts of pain every day, 53 (16%) reported that the pain was always present and six (2%) reported a few attacks of pain every hour. Of those respondents whose phantom limb pain remained constant over the years, 58 (40%) were suffering pain attacks a few times per month, 39 (28%) reported that the pain was present continuously, 27 (19%) had a few attacks per day, 15 (10%) reported only a few attacks per year and only five (3%) reported a few attacks per hour. When the pain started, it lasted a few seconds or minutes in 116 (40%) respondents reporting phantom pain, hours in 87 (30%) and days in 17 (6%), and 70 (24%) reported that the pain was variable in duration with no pattern. The most common description of the phantom pain feeling was stabbing pain (24.3%) and pins and needles (20.5%) (table 2).

## PHANTOM SENSATION *VS* PHANTOM PAIN

Three-hundred and fifty-two respondents reported the feeling of phantom sensation (66.8% of total respondents) and of these 273 (77.6%) reported phantom pain and phantom sensation. The strong relation between phantom pain and phantom sensation was obvious (chi-square=107.3 with 1 df, $P<0.00001$). We did not ask if phantom sensation preceded phantom pain. Respondents were asked to rate the intensity of their benign phantom sensation on the 0–10 scale (analogous to the visual analogue scale for pain). Sixty-three (17.9%) respondents reported phantom sensation but no phantom pain; mean phantom sensation intensity was 3.2 (SEM 0.31). Mean intensity of phantom sensation in respondents reporting phantom pain was 5.4 (0.17). This was significantly higher than the mean of 3.2 (0.31) reported by respondents who never reported phantom pain (fig. 2). The linear relationship between intensity of the usual phantom pain and phantom sensation intensity is shown in figure 3. There was a strong correlation between location of phantom limb sensation and phantom pain (chi-square=1562 with 196 df, $P<0.000001$) (table 3). Sixty-seven percent (67%) of respondents reporting phantom pain and phantom sensation reported exactly the same location for both sensation and pain. There was no relation between phantom sensation and site of amputation. We found that the intensity of phantom sensation was a significant predictor of the course of phantom pain in the future (time course), that is whether the phantom pain disappeard, decreased, remained the same or increased in the years after amputation. Of respondents reporting phantom pain with a phantom sensation intensity of 5 or less on the 0–10 scale, 61% said their phantom pain either decreased substantially or disappeared completely in due course. On the other hand, in respondents reporting phantom pain whose phantom sensation intensity was 5.1 and higher, 69% reported continued experience of phantom pain with the same intensity, while 3.7% reported increased intensity of pain. No respondent from the former

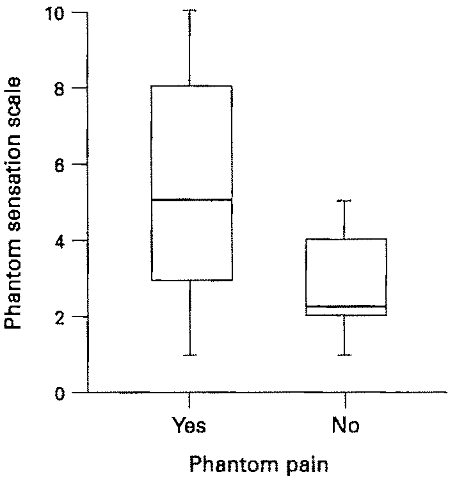

*Figure 2* Box plot showing intensity of phantom sensation in respondents reporting and not reporting phantom pain. The lower boundary of the box is the 25th percentile, and the upper boundary is the 75th percentile. The horizontal line inside the box represents the median. The whiskers are the largest and smallest values that are not outliers.

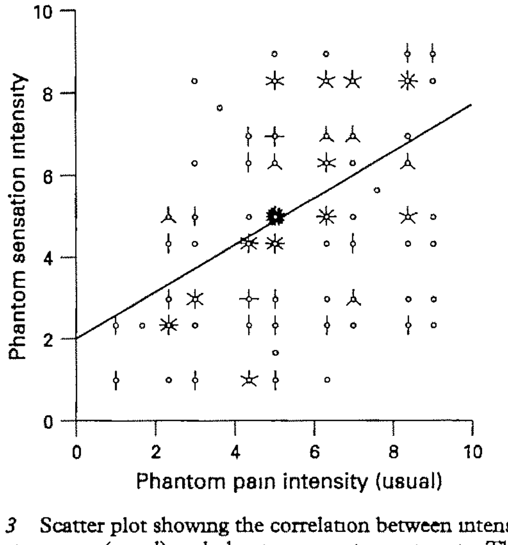

*Figure 3* Scatter plot showing the correlation between intensity of phantom pain (usual) and phantom sensation intensity. The number of petals in a sunflower represents the number of cases.

*Table 3* Site of phantom pain and phantom sensation. Note some respondents had more than one site of phantom limb pain and sensation

| Site | Phantom pain site (% of respondents) | Phantom sensation site (% of respondents) |
|---|---|---|
| Fingers/toes | 32 | 44 |
| Hand/foot | 45 | 46 |
| Wrist/ankle | 13 | 14 |
| Sole | 6 | 5 |
| Arm/leg | 16 | 12 |
| Elbow/knee | 6 | 4.5 |
| Near but not the stump | 7 | 2 6 |
| Old injury site | 1.8 | 1 |
| Whole arm/whole leg | 9 | 9 |

*Table 4* Relationship between phantom sensation intensity and phantom pain time course. PS=Phantom sensation, PP=phantom pain, %=percent of respondents

| PS intensity | PP disappeared | PP decreased | PP remained same | PP increased |
|---|---|---|---|---|
| 1–5 | 10.6% | 50.4% | 39% | 0% |
| 5.1–10 | 2.8% | 24.3% | 69.2% | 3.7% |

group reported increased pain intensity (chi-square=22.7 with 1 df, $P$=0.00001) (table 4).

In view of these significant relationships between phantom pain and phantom sensation, we were able to allocate respondents reporting phantom pain to one of three groups: group 1, 46 respondents reporting phantom pain with no phantom sensation (15% of respondents reporting phantom pain); group 2, 32 respondents reporting phantom pain and benign phantom sensation (10% of respondents reporting phantom pain); group 3, 237 respondents reporting phantom pain and uncomfortable phantom sensation (dysaesthesia) (75% of respondents reporting phantom pain). We found a significant difference between the three groups in relation to the time course of their phantom pain (chi-square=100.5 with 6 df, $P$=0.00001). Phantom limb pain disappeared or decreased in intensity in 39 (85%) respondents in group 1 in contrast with 21 (65.6%) and 103 (43.8%) respondents in groups 2 and 3, respectively. Only seven (15%) respondents in group 1 continued suffering phantom pain with the same intensity, compared with nine (28%) and 125 (53.2%) in groups 2 and 3, respectively (table 5).

One hundred and ninety-five (82%) respondents in group 3 experienced stump pain. This was significantly higher than the incidences in group 1 (28 (12%)) and group 2 (14 (6%)) (chi-square=16.6, with 6 df, $P$=0.0002). There was no significant difference in the intensity of stump pain or phantom limb pain between the three groups.

Phantom sensation intensity was significantly higher in group 3 (mean 5.7 (SEM 0.17)) compared with group 2 (2.6 (0.41)). There was a significant difference between the three groups in relation to phantom pain frequency (chi-square=31.9 with 8 df, $P$=0.0001). In groups 1 and 2, pain occurred mainly as a few attacks per year while in group 3 phantom pain was far more frequent, occurring as a few attacks every month. There was no difference between the three groups in their response to different methods of treatment.

### CORRELATION BETWEEN POSSIBLE PREDISPOSING FACTORS AND PHANTOM PAIN

There was no significant difference between those respondents reporting phantom pain and those not reporting phantom pain in relation to age at amputation (means 25.8 and 25.2 yr, respectively) ($P$=0.27). No significant difference was found between respondents reporting phantom pain and those not reporting phantom pain in relation to site of amputation (chi-square=5.5, 3 df, $P$=0.13) and pain in the limb before amputation (chi-square=10.6 with 4 df, $P$=0.3). The incidence of phantom limb pain was not higher in respondents who had more than one limb amputation (chi-square=0.007 with 1 df, $P$=0.93).

### POST-AMPUTATION PREDICTORS OF PERSISTENCE OF PHANTOM PAIN

There was a significant difference between respondents reporting phantom pain and not reporting phantom pain in relation to age (mean 70 and 72.4 yr, $P$=0.016). However, this difference was not clinically significant. There were no significant differences between respondents reporting phantom pain and those not reporting phantom pain concerning the use of a prosthesis ($P$=0.6) or number of hours per day the prosthesis was used (means 13.2, 13.6 h, respectively, $P$=0.1). Only 20 (3.8%) respondents did not use their prosthesis. The main reasons for not using it were stump problems (34%), ill health (24%) and clumsiness (22%), especially in upper limb amputees. Only 8% reported aggravation of phantom limb pain with the use of a prosthesis.

*Table 5* Relationship between the three groups of presentation of the sample and the time course of phantom pain. PP=phantom pain, PS=phantom sensation, %=percent of respondents reporting phantom pain

| | PP with no PS (Group 1) | PP with benign PS (Group 2) | PP with uncomfortable PS (dysaesthesia) (Group 3) |
|---|---|---|---|
| Respondents reporting PP | 46 | 32 | 237 |
| PP disappeared | 29 (63%) | 5 (15.6%) | 15 (6.4%) |
| PP decreased | 10 (21.7%) | 16 (50%) | 88 (37.4%) |
| PP remained same | 7 (15.2%) | 9 (28.1%) | 125 (53.2%) |
| PP increased | 0 (0%) | 2 (6.3%) | 7 (3%) |

### PAIN SENSITIVITY AND ATTITUDE TOWARDS USE OF MEDICAL TREATMENT FOR PAIN NOT RELATED TO THE AMPUTATION

There was no significant difference between respondents reporting and not reporting phantom pain concerning headache intensity before taking medication (means 6.4 and 6.1, $P=0.42$), and duration of headache before taking medication (means 2.2 and 2.0, $P=0.5$).

### PHANTOM PAIN TREATMENT

One hundred and forty-nine respondents reporting phantom pain discussed their pain with their family doctor. There was a significant difference in the duration, frequency and worst pain intensity between respondents discussing and respondents not discussing the pain. Respondents who reported phantom pain lasting hours, days or of variable pattern tended to discuss their pain (chi-square=24.8 with 4 df, $P=0.00005$). Their worst phantom pain intensity was significantly higher (mean 8.7) ($P<0.0001$). Respondents reporting phantom pain episodes of a few times every year were the least likely to discuss their phantom pain (chi-square=16.2, with 3 df, $P=0.001$). Forty-nine respondents who discussed the pain with their doctors were told that there was no treatment to help the pain. The remainder were told the following: 20 respondents "pain is expected after amputation"; 17 respondents "the pain is nerve pain"; eight respondents "the pain is in their mind"; 11 respondents "the pain will go away"; six respondents "the stump is the cause of phantom pain" and one respondent was told "this pain will never go away". Seventy-five respondents who discussed their phantom pain with their doctor were prescribed analgesics, 39 were offered nothing and only 17 respondents were referred to a pain relief clinic.

*Table 6* Methods used for treatment of phantom pain and patient satisfaction. Others=Cryotherapy, cordotomy, nerve block, ointments and hitting the stump with a wooden mallet. *All respondents who were offered no treatment returned the question "were you satisfied with your treatment?" unanswered

| Treatment type | Amputees received treatment | Amputees were satisfied with treatment |
|---|---|---|
| TENS | 26 (36%) | 11 (42.3%) |
| Operation on the stump | 12 (16.6%) | 5 (41.6%) |
| Injections of the stump | 11 (15%) | 1 (9%) |
| Sympathectomy | 8 (11%) | 3 (37.5%) |
| Acupuncture | 3 (4%) | 0 |
| Others | 15 (20.8%) | 0 |
| Nothing | 8 (11%) | N/A* |

*Table 7* Medication used for phantom pain treatment and patient satisfaction. Simple analgesics=paracetamol, compound analgesics=paracetamol and opioid, NSAID=non-steroidal anti-inflammatory drugs, anticonvulsants=carbamezapine, antidepressants=amitriptyline

| Type of medicine | Respondents using it | Respondents satisfied |
|---|---|---|
| Simple analgesics | 96 (53%) | 45 (47%) |
| Compound analgesics | 67 (37%) | 42 (63%) |
| NSAID | 27 (15%) | 20 (74%) |
| Anticonvulsants | 12 (6.6%) | 3 (25%) |
| Opioids | 10 (5.5%) | 4 (40%) |
| Antidepressants | 2 (1%) | 0 |
| Alcohol | 42 | 31 (74%) (helpful) |

Seventy-two respondents reporting phantom pain asked for treatment for their phantom pain: eight (11%) respondents were offered nothing and 26 (36%) received transcutaneous electric nerve stimulation (TENS), of whom 11 (42%) expressed satisfaction with the treatment, including three who reported that it partially helped and another two who reported that it was extremely helpful (table 6). There was no significant difference in phantom pain intensity between respondents who reported satisfaction and those who did not report satisfaction with (TENS) treatment. In eight respondents of those who were satisfied with TENS treatment, it was used in conjunction with other methods of pain control. However, they reported their satisfaction with TENS treatment alone. Other treatments included different operations on the stump in 12 (16.6%) respondents, injections of the stump in 11 respondents (15%) and sympathectomy in eight (11%) respondents. Reasonable satisfaction was reported with operations on the stump and sympathectomy, with low satisfaction from nerve blocks (table 6).

One hundred and eighty-two respondents reporting phantom pain were taking medication for their pain at the time of the study. Ninety-six respondents were taking simple analgesics (paracetamol); 45 (47%) reported satisfaction with the treatment. Compound analgesics (paracetamol with an opioid) were taken by 67 respondents, with 42 (63%) reporting satisfaction. Although only 27 respondents were taking non-steroidal anti-inflammatory drugs (including aspirin), 20 (74%) stated their satisfaction with its phantom pain controlling effect (table 7). Forty-two respondents took alcohol to help their pain, of whom 31 (74%) reported that it was helpful.

Two hundred and twenty-three respondents reporting phantom pain did not wish to be treated at present. Sixty-five (29%) of those respondents reported the pain was not bad enough to require treatment; 32 (14%) reported their pain was not frequent enough; 18 (8%) had no more pain; 26 (12%) reported that the results of treatment were not encouraging among the amputee community; 35 (16%) were used to the pain; 22 (10%) thought they were too old to try new treatments; and 17 (8%) feared the complications of various methods of treatment.

*Table 8* Stump pain treatment. Miscellaneous=hitting the stump, massage, creams, acupuncture

| Type of treatment | Respondents |
|---|---|
| Operation on the stump | 14 (18 7%) |
| TENS | 12 (16%) |
| Injections | 12 (16%) |
| Alterations of the artificial limb | 7 (9.3%) |
| Sympathectomy | 3 (4%) |
| Miscellaneous | 27 (36%) |

### STUMP PAIN TREATMENT

Only 75 (22%) respondents who reported stump pain received treatment (table 8). Interestingly, hitting the stump with a wooden mallet, which is described as the oldest method for stump pain treatment, was still used by several respondents. One hundred and eighty-three (55%) of the respondents reporting stump pain were taking analgesics.

## Discussion

This is the second largest survey on phantom limb pain and stump pain after the survey reported by Sherman, Sherman and Parker in 1984.[4] The results of our study are of interest in three aspects. First, it is the largest British survey on chronic pain related to traumatic limb amputation. Second, the long-standing amputees studied presented us with ample information to assess the time course of phantom pain and stump pain. Third, the excellent response provided reliable information to address the problems of phantom limb and stump pain in amputees.

In designing a mailing survey, the length of the questionnaire in relation to the number of questions asked and the total number of pages sent to the potential respondent, is a major concern. In our study, which consisted of a relatively long questionnaire, we achieved a response rate of 89%. This highlights two interesting points: first, the response to a survey is related directly to the impact of the subject under investigation on the individual's life; second, the characteristics of the sample play an important role in their response, for instance the age of the amputees we studied. As war pensioners we anticipated that they have sufficient spare time to respond.

Fifty-five percent of respondents reported unambiguously the experience of phantom pain with a mean pain intensity of 5.6 on a 0–10 scale; this suggests that a considerable number of amputees suffer from this perplexing pain at least at some stage after amputation. Our result is similar to the 54% frequency reported in 1987 by Krebs and colleagues who followed-up 86 patients with limb amputations caused mainly by peripheral occlusive vascular diseases for 7 yr.[5] Riddoch reported a similar frequency in 1941 in traumatic and surgical amputations.[7] It seems that phantom pain has the same rate of occurrence in traumatic and other forms of amputation and it may be a persistent condition that stays with the amputee for the remainder of life as approximately 50% of respondents reporting phantom pain were in the worst pain for a long duration.

Our results showed a similar frequency of stump pain compared with phantom limb pain. However, stump pain intensity was higher. The six most common causes of stump pain are: prosthogenic, neurogenic, arthrogenic, sympathogenic, referred and abnormal stump tissue.[9] Most of these causes can be treated. It seems that we need to address the problem of stump pain and phantom limb pain when treating limb amputation related pain.

Phantom pain may be expected to decrease or even disappear with time.[10] Almost 50% of respondents suffering from phantom pain reported a substantial decrease to complete alleviation of pain, suggesting that this could be true in some cases of long-standing amputations. However, 47% of amputees continued to experience pain, indicating the seriousness of the problem in the amputee population.

Approximately 50% of respondents reporting phantom pain discussed their pain with their family doctor. These respondents suffered the most pain for long durations with frequent attacks. One might expect that amputees with phantom pain of such characteristics would be referred to pain clinics where they may have greater access to therapies provided by specialists in the field of chronic pain management. However, only 17 amputees were referred to such centres. This may prevent patients from receiving adequate care. There is clear evidence that phantom pain is not an easy condition to manage even when therapy is provided by specialists. The problem is not if patients try therapies but if they receive them in a structured manner.[11]

Sherman, Sherman and Parker[4] reported in 1984 the use of TENS in 20 of 2145 (0.9%) amputees with phantom pain. TENS at that time was expensive and rarely available outside pain clinics. At present they are used by physiotherapists, nurses, palliative care specialists and pain clinicians. Our finding that of the 72 amputees with phantom pain who requested treatment, 26 (36%) received TENS of whom 11 (42%) experienced satisfactory pain relief is significant as we assume that at least a few of those had the treatment for more than 1 yr. These patients were not satisfied with other therapies or even concomitant therapies, but only with TENS. This does not suggest satisfaction with treatment in general or the quality of care or the carers. It is also a common experience that if TENS is ineffective, it is discontinued even if it is not returned. TENS is often discontinued despite efficacy because it is inconvenient or irritant, or the efficacy is not great enough to outweigh the inconvenience or intrusive sensation. TENS is a simple, safe and re-usable first-line treatment.[12] It can be used long term with no risk of serious adverse effects.[13] Perhaps the principal message from these results is that TENS is at least as effective as any other therapy and as it is neither destructive nor expensive, it should be the treatment of first choice.

It seems that analgesic medicine has a useful role in the relief of phantom pain. Paracetamol was the most commonly used drug. However, the synergistic action of paracetamol and an opioid showed increased satisfaction with pain relief. NSAID were successful in 74% of 27 patients in our sample. In acute pain there is a growing body of evidence in favour of a central mechanism for the anti-inflammatory and analgesic effects.[14] NSAID have been shown to exert a direct spinal action by blocking the excessive sensitivity to pain (hyperalgesia) induced by activation of spinal glutamate and substance P receptors.[15] There is also strong evidence that NSAID work by changing 5-HT concentrations in the central nervous system.[16] Information on chronic pain is not yet available.

The development of phantom limb pain after amputation has been the subject of much discussion. Our work has added a new finding to the debate, namely the strong correlation between intensity of mechanical phantoms and severity of phantom limb pain. Therefore, it appears that nervous activity responsible for either sensation is mediated along the same central pathway.

The first point of convergence from tactile and nociceptive primary afferents is at the level of the wide dynamic range neurones in the dorsal horn. It is from this level rather than from higher levels of the pain pathway that central phantom limb pain is most likely to originate; there is animal evidence that after experimental division of the dorsal columns there is very little adaptive reorganization of the cerebral cortex.[17]

Yang and colleagues[18] and Aglioti, Bonazzi and Cortese[19] observed that phantom limb pain may be projected to parts of the body from parts of the body previously serving the amputated limb. These authors interpreted their findings as caused by cortical plasticity; their findings are, however, also consistent with the well documented concept of reorganization involving sprouting into adjacent laminae in the somatotopically organized dorsal horn[20] after transection of peripheral nerves in animal experiments.[21] In essence, somatic central phantom limb pain may be a condition of pathologically increased gain in the wide dynamic range neurones.

We conclude that phantom pain is a major problem as 47% of suffering amputees reported continuing pain. The more treatable stump pain was equally common. TENS, analgesics and NSAID seemed to have a role in the treatment of phantom limb pain. The relation between phantom pain and phantom sensation is still not clear and requires further investigation.

## Acknowledgement

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# Low molecular weight heparin associated with spinal anaesthesia and gradual compression stockings in total hip replacement surgery†

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## Summary

The benefit/risk ratio of administering heparin during spinal anaesthesia in patients undergoing total hip replacement (THR) has not been studied widely. We conducted a prospective, randomized, double-blind study to compare low molecular weight heparin (LMWH) for 10 days and placebo in patients undergoing THR performed under spinal anaesthesia associated with gradual compression stockings. Efficacy was assessed by systematic bilateral ascending venography on day 10±2 in a sequential analysis. Among the 170 patients enrolled, data were available in 153 patients. In the LMWH group (*n*=78) the total incidence of deep vein thrombosis (DVT) was 14.1% compared with 37.3% in the placebo group (*n*=75) (*P*=0.0016). No gross neurological sequelae were observed during the study. This study showed that the addition of LMWH in patients undergoing THR under spinal anaesthesia and wearing gradual compression stockings significantly decreased the incidence of venogram-proved DVT. (*Br. J. Anaesth.* 1997; **78**: 660–665).

**Key words**
Surgery, orthopaedic. Anaesthetic techniques, subarachnoid. Complications, deep vein thrombosis. Blood, anticoagulants, heparin.

It is well recognized that patients undergoing total hip replacement surgery (THR) are at high risk of developing venous thromboembolism. Fatal pulmonary embolism may occur in 1–5% of these patients.[1–3] Without thromboprophylaxis, incidences of venogram-proved deep vein thrombosis (DVT) of up to 50% have been reported.[4] Several clinical studies have demonstrated the effectiveness and high benefit/risk ratio of low molecular weight heparins (LMWH) in the prophylaxis of DVT,[4–7] and meta-analyses have confirmed their role in patients undergoing orthopaedic surgery.[8 9] Central neural block (extradural anaesthesia or subarachnoid anaesthesia) is used widely in orthopaedic surgery. Spinal anaesthesia has been shown in fracture and elective hip surgery to moderately reduce postoperative DVT.[10] Winter-Christensen and colleagues[11] showed in 55 THR patients that extradural anaesthesia alone was as effective in preventing DVT as unfractionated heparin in combination with extradural anaesthesia. However, the association of heparin and central neural block remains questionable because of the potential risk of spinal haematoma.[12] A consensus conference, held in Europe in 1991, suggested that the benefit/risk ratio of this association should be reassessed.[13] This prospective, randomized, double-blind study was therefore designed to assess the benefit/risk ratio of LMWH in addition to spinal anaesthesia and gradual compression stockings in THR surgery.

## Patients and methods

We considered eligible for the study consecutive patients aged more than 18 yr, weighing 45–95 kg, undergoing primary THR surgery under regional anaesthesia (subarachnoïd block and catheter removed at the end of the surgical procedure), wearing gradual compression stockings (started the day before surgery).

Exclusion criteria were: re-operation for THR, surgery under general anaesthesia, patients under nail extension before surgery, history of DVT, pulmonary embolism, or both, hepatic or renal insufficiency, lung or heart failure, ASA status more than III, haemorrhagic disorders contraindicating the use of antithrombotic drugs (active ulcerative disease, uncontrolled arterial hypertension, stroke within the previous 6 months or other known haemorrhagic disorders), occurrence of a bloody tap during spinal

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puncture, platelet count less than $100 \times 10^9$ litre$^{-1}$, history of heparin-associated thrombocytopenia or allergic reactions to heparin, low molecular weight heparin or to radiocontrast agents, and women with childbearing potential. In addition, patients were not included if they received heparin for more than 24 h before surgery, oral anticoagulant treatment within 3 days, antiplatelet drugs within 8 days or non-steroidal anti-inflammatory agents within 2 days before surgery.

A prospective, double-blind, randomized, placebo-controlled study was carried out on two parallel groups of patients in 11 participating centres. Patients were selected to enter the study before the surgical procedure if they completed the pre-screening criteria, and randomization was made at the end of the surgical procedure at 6±1 h after spinal puncture. This procedure aimed to exclude pre-screened patients needing general anaesthesia during surgery. Patients were allocated to receive subcutaneously, once daily, for 10±2 days either LMWH or placebo. All patients underwent daily clinical evaluation and systematic bilateral ultrasonography of the lower extremities on treatment days 3 and 6. All patients underwent systematic bilateral ascending contrast venography on day 10±2 after surgery, or earlier if indicated. Patients with negative venography on day 10±2 were then given, a once-daily dose of LMWH s.c. (open label enoxaparin 40 mg) for 28 days after hospital discharge as long-term prophylaxis because these patients were considered at high risk of DVT within the month following surgery.[13] Those with evidence of DVT detected by the investigator on systematic venography were treated using the usual therapeutic regimens. All patients were scheduled for a 3-month post-surgery follow-up. All clinical suspicions of a thromboembolic event during this follow-up period were documented by ultrasonography or venography for DVT, and by ventilation–perfusion lung scan or angiography for pulmonary embolism.

This study was conducted in accordance with the Declaration of Helsinki, European Good Clinical Practice and French Law. The study was approved by the Ethics Committee of La Pitié-Salpêtrière Hospital, Paris, France, and written informed consent was obtained from all patients before randomization.

### THERAPEUTIC REGIMENS

Eligible patients operated on under spinal anaesthesia and wearing gradual compression stockings (Ted stockings provided by Kendall) were allocated randomly to receive either LMWH or placebo, using a computer-generated randomization schedule, which was equilibrated by study centre and balanced in blocks of four patients. Patients in the LMWH group received, once daily, enoxaparin 40 mg (0.4 ml) s.c., corresponding to 4000 iu of anti-Xa, for 10±2 days. Patients in the control group received subcutaneously, once daily, a 0.4-ml injection of saline s.c. (3.6 mg of sodium chloride in 0.4 ml of infusion water) for 10±2 days.

### OUTCOME MEASURES

The primary efficacy outcome was defined as the occurrence of postoperative venous thromboembolic complications (confirmed DVT or pulmonary embolism) during the 10±2 postoperative days after surgery. The primary study conclusions for efficacy were based on intent to treat analysis in patients with adequate radiographic examinations reassessed by an independent central Reading Committee for venographies, angiographies or lung scans, and if necessary by a third expert from the Data and Safety Monitoring Review Board. All venograms were evaluated by two independent radiologists who were unaware of the treatment. The venograms were considered positive when a constant intraluminal filling defect was present in at least two different positions. DVT was classified as proximal when the thrombus was in the popliteal vein or above, and as distal when the thrombus was in the calf vein. Muscle veins were also taken into account in addition to DVT for safety purposes considering the estimated risk of developing a visualized thrombus in a placebo group. All patients with proximal, distal or muscle thrombi were considered as having DVT.

The secondary efficacy and safety outcomes were defined as occurrence of clinically suspected venous thromboembolic events, major or minor haemorrhagic episodes or any other serious adverse event (including death, life-threatening events and events that resulted in prolonged hospitalization or re-hospitalization) within the 3-month follow-up.

Haemorrhage was classified as major if it was overt and associated with either a decrease in haemoglobin of 2 g dl$^{-1}$ or more, a need for transfusion of 2 u. or more of packed red blood cells, if it was retroperitoneal or intracranial, or if it led to surgical reintervention or death. Haemorrhage was defined as minor if it was overt but did not meet the other criteria for major haemorrhage. Intra- and postoperative blood loss was also calculated. The potential occurrence of spinal haematoma was assessed by daily patient examination performed by an anaesthetist during hospitalization. No systematic neurological assessments were required except in cases of clinical symptoms suggesting neural compression such as sensitive or motor deficit associated with back pain. The postoperative blood loss calculation was performed by the standardized method of Toy and colleagues.[14] Measures of wound haematoma width were recorded daily. Blood samples for measurement of haemoglobin concentration and platelet count were obtained before surgery, and on days 3, 6 and 10±2.

### STATISTICAL ANALYSIS

This study was conducted as a closed sequential trial. Sample size evaluation was based on the assumption of an expected incidence of DVT of 15% for the LMWH group and 25% for the control group. Considering a type I error of 5% and type II error of 20%, it was calculated that a total number of 500 patients (250 in each group) would be needed to detect such a difference. In this study the statistical

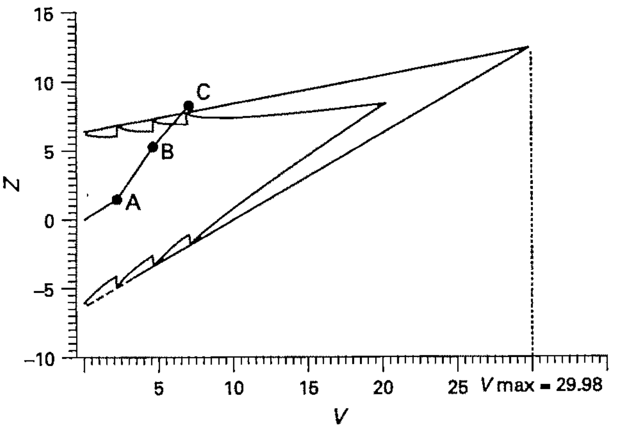

*Figure 1* Triangular test results (presentation of test boundaries). A=first analysis in 51 patients (46 evaluable); B=second analysis in 109 patients (99 evaluable); C=third analysis in 163 patients (147 evaluable). $Z$=efficacy variation between the two treatment groups; $V$=Fisher's information for the triangular test. Note that of the 170 included patients, seven patients overran at the time that the Data and Safety Monitoring Review Board recommended cessation.

*Table 1* Patient characteristics (mean (SD) [range] or number)

| | LMWH ($n$=85) | Placebo ($n$=85) |
|---|---|---|
| Age (yr) | 67.2 [36.9–89.21] | 67.2 [31.6–87.5] |
| Sex (M/F) | 58/27 | 41/44 |
| Weight (kg) | 74.4 (12.1) [49–95] | 71.4 (11.1) [45–95] |
| Height (cm) | 167.5 (6.2) [148–178] | 165.6 (7.1) [150–186] |
| Body mass index ($kg\ m^{-2}$) | 26.4 (3.75) [18.4–35] | 25.9 (3.2) [17.6–34.3] |

*Table 2* Baseline charateristics of the surgical and anaesthetic procedure

| | LMWH ($n$=85) | Placebo ($n$=85) |
|---|---|---|
| Central neural block | | |
| Simple/continued | 82/3 | 82/3 |
| Anaesthetic drug | | |
| Bupivacaine | | |
| Isobar | 28 | 27 |
| Hyperbar | 55 | 55 |
| Lignocaine | 1 | 0 |
| Amethocaine | 1 | 3 |
| Adrenaline | 10 | 8 |
| Reinjection | 6 | 3 |
| Catheter use | 3 | 2 |
| Need of sedation | 0 | 0 |
| Side of procedure | | |
| Left/right | 40/45 | 49/36 |
| Surgical approach | | |
| Anterior | 21 | 18 |
| Posterior | 61 | 60 |
| External | 2 | 6 |
| Antero-external | 1 | 1 |
| Osteotomy | | |
| With/without | 3/82 | 4/81 |
| Type of THR | | |
| Femur and acetabulum | 85 | 85 |
| Femoral cemental prosthesis | | |
| Yes/No | 63/22 | 57/28 |
| Duration of surgery (min) (mean (SD)) | 70.1 (27.3) | 69.2 (27.9) |

procedure was a sequential grouped analysis using the simple triangular test procedure[15] in which the final sample size is not fixed in advance. In this procedure, data concerning the primary efficacy endpoint were analysed after every 50 patients. In these conditions, the maximum final sample size could be a total number of 750 patients (375 patients in each group), corresponding to a maximum number of 15 inspections. Two statistical assessments were calculated: the first was a cumulative measure of the difference between the LMWH group and the control group, the second was a measure of the information available in the study. A plot of these two statistics was maintained: these values were the coordinates in the sequential design for the analysis. At each analysis, one point was drawn on the triangle shown in figure 1 and the global results for efficacy and safety were presented to the Data and Safety Monitoring Review Board. The pattern of all the points created was termed the sample path. When this path remained inside the triangle, the study had to be continued but if the sample path increased or decreased, the study had to be stopped. The sequential analyses were computed by PEST version 2.2. Other qualitative data were analysed by the chi-square test or Fisher's exact test, and the Student's $t$ test was used for quantitative data. All tests were two-tailed with a 5% level of significance. These analyses were performed on the statistical software SAS version 6.08.

## Results

From March 1993 to July 1994, 170 patients, 85 in each treatment group, having undergone THR under spinal anaesthesia, were included in the study and received at least one dose of the study medication. These patients were all considered in the safety analysis. Seven of the 170 patients were ongoing at the time of the decision to stop the inclusion recommended by the Data and Safety Monitoring Board. They were considered as overrunning patients and did not appear in the third sequential analysis ($n$=163). Among the 170 included patients, 17 patients (seven in the LMWH group and 10 in the control group) were not considered in the intent-to-treat analysis of efficacy, because venography could not be performed (12 patients: four in the LMWH group and eight in the control group) or because venography was found to be inadequate by the review committee (five patients: three in the LMWH group and two in the control group). Finally, a total of 153 patients were analysed on an intent-to-treat basis (78 in the LMWH group and 75 in the control group). The two treatment groups did not differ in baseline characteristics, excepted for gender (table 1). This factor, which was taken into account in the primary analysis of efficacy, was not found to affect the results of this analysis. The main characteristics of the surgical and anaesthetic procedure are presented in table 2.

### THROMBOEMBOLIC COMPLICATIONS

There were no deaths or clinical pulmonary emboli during the study. A total of 39 patients of the 153 evaluable patients (25.5%) presented with venogram-proved DVT of the lower extremities (table 3). Most were asymptomatic and only two

*Table 3* Incidence of venogram-proved DVT on day 10±2. $^{**}P<0.01$

| Thrombus site | LMWH ($n$=78) | Placebo ($n$=75) | Overall ($n$=153) |
|---|---|---|---|
| Proximal DVT | 2 | 12 | 14 |
| Distal DVT | 8 | 13 | 21 |
| Muscular VT | 1 | 3 | 4 |
| Total DVT$^{**}$ | 11 (14.1%) | 28 (37.3%) | 39 (25.5%) |

patients (one patient in each group) presented clinical signs of DVT which were confirmed by venography. Overall, the incidence of venous thrombosis on day 10±2 was 14.1% in the LMWH group (95% confidence interval 6–22%), compared with 37.3% (25–47%) in the control group. This difference was statistically significant ($P$=0.0016) for the triangular test corrected according to the 5% significance level adopted (table 3). None of the 17 excluded patients who did not undergo adequate venography were found to present with clinical signs suggesting DVT. No patient variable was found to affect overall comparison of efficacy outcome of the evaluable patients between the two treatment groups. Of the 39 DVT, eight were bilateral, 20 were in the operated legs and 11 were on the opposite side. Most were detected on systematic examination at day 10±2, whereas seven were detected by ultrasonography before the end of the treatment period (six in the control group and one in the LMWH group).

### BLEEDING COMPLICATIONS

No gross neurological sequelae were observed. Overall, major haemorrhage occurred in 1.2% and minor haemorrhages, including wound haematomas smaller than 1 cm, in 31.2% of patients (table 4). Two patients were considered to present with major haemorrhage: one patient in the LMWH group presented with postoperative haemorrhage at the surgical site on day 6, with a decrease in haemoglobin concentration of more than 4 g $dl^{-1}$, and requiring transfusion of 2 u. of packed red blood cells; and one patient in the control group presented with postoperative haemorrhage on day 3 through wound drainage with a decrease in haemoglobin concentration of more than 4 g $dl^{-1}$ and requiring transfusion of 2 u. of packed red blood cells, but no reintervention. Thirty-two patients in the LMWH group (37.6%) and 21 patients in the control group (24.7%) experienced minor haemorrhage ($P$=0.04). Haemorrhage did not lead to surgical reoperation or premature discontinuation of the study in any patient. There were no differences between the two groups in perioperative blood loss (table 4). Of the 170 patients, 23 received homologous transfusions (13.5%): 16 in the LMWH group and seven in the control group ($P$=0.044).

### OTHER ADVERSE EVENTS (FROM DAY 1 TO DAY 10±2)

There were no study withdrawals as a result of adverse events other than DVT or haemorrhages. A total of 45 patients with an unexpected adverse event were observed during the study: 24 patients in the LMWH group and 21 patients in the control group. The principal causes were subluxation of prosthesis in three patients requiring reintervention under general anaesthesia, symptomatic anaemia requiring transfusions in 11 cases, infection (wound infection or general infection) in 12 patients and other symptoms in 19 patients. Among the total number of unexpected adverse event, only five cases (three in the LMWH group and two in the control group) were considered as "possibly" or "probably" related to the study treatment. The remaining cases were considered as mild to moderate in intensity, and resolved within a few days even though the study treatment was maintained.

### 3-MONTH FOLLOW-UP PERIOD (FROM DAY 12 TO DAY 90)

A total of 169 patients (85 in the LMWH group and 84 in the control group) underwent post-surgical follow-up at 3 months (one patient was lost to follow-up). No deaths or thromboembolic events were observed during this period. Fourteen patients presented with further adverse events: six in the LMWH group and eight in the control group. The principal causes were subluxation of prosthesis after day 10 in four patients requiring reintervention under general anaesthesia, infection in two patients and other symptoms in eight patients.

### LABORATORY TESTS

There were no significant differences between the two groups in absolute and relative changes in red cells and haemoglobin concentration from day 0 to

*Table 4* Bleeding complications (mean (SD) or number)

| | LMWH | Placebo | $P$ |
|---|---|---|---|
| Spinal haematoma ($n$) | 0 | 0 | |
| Major haemorrhages ($n$) | 1 | 1 | |
| Wound haematomas ($n$) | | | |
| <1 cm | 5 | 8 | |
| 1–5 cm | 11 | 4 | |
| >5 cm | 17 | 8 | |
| Total | 33 | 20 | 0.04 |
| Intraoperative blood loss (ml) | 395 (133.1) | 422 (122.9) | 0.65 |
| Postoperative blood loss (ml) | 783.4 (409.4) | 790.4 (381.7) | 0.90 |
| Global calculated blood loss (ml) | 1538 (928.9) | 1399.7 (928.9) | 0.40 |
| Transfusion rate (day 1 to day 12) | 18.8% | 8.2% | 0.044 |

day 10±2. No thrombocytopenia occurred in the postoperative period.

## Discussion

We have demonstrated that in patients undergoing THR under spinal anaesthesia, the use of LMWH prophylaxis associated with gradual compression stockings significantly decreased the incidence of DVT. The combination of spinal anaesthesia and gradual compression stockings alone, without LMWH, did not provide sufficient antithrombotic prophylaxis. No symptomatic pulmonary emboli were observed in either group.

Many clinical studies[4–7] and meta-analyses[8 9] have established that the use of LMWH is associated with an improved benefit/risk ratio compared with dextran,[16] unfractionated heparin[5–7] or oral anticoagulants[17] in orthopaedic surgery. Spinal or extradural anaesthesia has also been shown to decrease the incidence of postoperative DVT.[18–20] This effect can be explained by the vasodilatation induced by the pharmacological blocking of the sympathetic system resulting in increased venous blood flow in the lower extremities,[21] the effect of local anaesthetics[22 23] and subsequent haemodilution.[24] This has been confirmed recently in a review by Prins and Hirsh in fracture and elective hip surgery.[10] Despite a reduction in the incidence of postoperative DVT (without prophylaxis) of 46–55%, this effect remains controversial.

Another study in THR patients showed a much lower incidence of venogram-proved DVT (12%) after operation under extradural anaesthesia.[25] In patients with a fractured hip, a meta-analysis recently reported a risk reduction (odds ratio) for DVT four times lower with spinal anaesthesia in comparison with general anaesthesia,[26] and a prospective study in patients treated before and after operation with LMWH was unable to find any difference in the rate of DVT between patients operated on under general anaesthesia and those who underwent central neural block.[27] The antithrombotic effect is probably less than that reported initially by Modig and colleagues.[18 24 28] Our study represents one of the largest DVT prophylaxis studies in patients operated on under central neural block. Despite the use of central neural block, associated with gradual compression stockings, the incidence of DVT was 37.3% in the control group on day 10±2 after operation. A placebo group was considered to be justified because of the following reasons: all patients wore gradual compression stockings which, although insufficient in high-risk patients, have a proven antithrombotic effect[29–31]; patients were monitored closely by daily clinical examination, by Duplex scanning performed on day 3 and day 6, and by bilateral ascending venography performed on day 10±2; sequential analysis was performed after every 50 patients in order to assess blindly the DVT rate in both groups, so that the study could be interrupted as soon as a significant difference was noted between the two groups.

In our study, LMWH prophylaxis significantly reduced the rate of DVT to 14.1%, which is close to the generally reported incidence in such patients.[8 9] Although in Europe the dosage regimen of enoxaparin 40 mg s.c once daily, beginning before operation, is commonly approved for the prevention of postoperative DVT in THR patients,[6] a regimen beginning after operation was chosen in accordance with the recommendations issued by the consensus conference for thromboembolic diseases held in 1991.[13] The risk of extradural or subarachnoid haematoma induced by preoperative LMWH and central neural block is probably very low. Tryba estimated the risk for a spinal haematoma after central neural block to be 1:150 000 after extradural anaesthesia and 1:220 000 after spinal anaesthesia.[32] However, the severity of neurological consequences has to be considered carefully and case reports are still published. A recent literature search reported 61 cases of extradural or spinal haematoma involving central neural block.[12] Forty-two patients had a clotting disorder or were treated with anticoagulants without specification of dose. This incidence is probably underestimated because many of these cases are not reported. This study was not designed specifically to assess the risk of spinal haemorrhage with the combination of LMWH and central neural block, as specific neurological assessments were not performed and the study population was too small to demonstrate a valid difference in the incidence of spinal haematoma. Although no clinical symptoms suggesting a spinal haematoma were observed in our study, the use of extradural or spinal anaesthesia in patients receiving a preoperative dose of LMWH remains a concern.

The frequency of postoperative bleeding complications, including wound haematoma, is believed to increase in heparin-treated patients. This is the main reason for the reluctance of many surgical teams to use heparin prophylaxis. The results of this study confirmed this observation, although there was no difference between the two groups in the incidence of major haemorrhage. Patients in the LMWH group experienced significantly more wound haematomas than in the control group. However, there were no discontinuations of study treatment or surgical reinterventions related to haematoma in either group. The standard postoperative blood loss calculation[14] taking into consideration the perioperative period until day 3, showed no difference between the two groups. However, the global transfusion rate observed in this study appeared lower than that reported for THR surgery. This could be explained by the type of anaesthesia as noted in a recent meta-analysis.[33] When comparing the transfusion rate between the two groups, the observed difference was in favour of the control group, as expected.

In conclusion, spinal anaesthesia during THR surgery in association with gradual compression stockings alone was not sufficient to protect against the risk of postoperative DVT. The addition of LMWH beginning after operation reduced the risk of venogram-proved DVT and demonstrated an acceptable benefit/risk ratio compared with placebo.

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# Intrathecal infusion of bupivacaine with or without morphine for postoperative analgesia after hip and knee arthroplasty

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## Summary

Postoperative pain after major orthopaedic operations can be controlled by continuous intrathecal administration of opioids or local anaesthetics. Effective intrathecal analgesia can be achieved through synergism of low doses of the two analgesic drugs and, possibly, less drug-related adverse effects. Therefore, we have evaluated the usefulness of a combined low-dose bupivacaine and morphine infusion in patients undergoing hip and knee arthroplasty. Spinal anaesthesia was induced in 55 ASA I–III patients with 0.5% bupivacaine 2 ml via a 28-gauge spinal catheter (L3–4 interspace) and 0.5-ml increments were given if needed. Intrathecal 24-h infusions consisted of bupivacaine 2 mg $h^{-1}$ alone ($n=18$), bupivacaine 1 mg $h^{-1}$ alone ($n=18$) or bupivacaine 1 mg $h^{-1}$ combined with morphine 8 μg $h^{-1}$ ($n=19$). The interview after 3, 6, 12 and 24 h included assessment of pain at rest and on movement (VAS scale), occurrence of sensory and motor block and nausea/vomiting. Bupivacaine 1 mg $h^{-1}$ combined with an infusion of morphine provided as good postoperative analgesia as bupivacaine 2 mg $h^{-1}$, but motor block disappeared earlier ($P=0.01$). Patients in the bupivacaine 1-mg $h^{-1}$ group required more supplementary doses of oxycodone i.m. than the other groups ($P=0.04$). Time to first oxycodone dose from the start of intrathecal infusion did not differ between groups. The frequency of nausea and vomiting was similar in all groups. In spite of this, antiemetic medication was required more often in the bupivacaine 1-mg $h^{-1}$ group (possible because of opioid rescue medication). On the ward, one patient in the bupivacaine 2-mg $h^{-1}$ group experienced a new increase in sensory block with concomitant hypotension. One patient in the same group had minor decubitus on the heel of the operated leg, probably because of prolonged motor block. We conclude that intrathecal infusion of a combination of bupivacaine 1 mg $h^{-1}$ and morphine 8 μg $h^{-1}$ produced adequate postoperative analgesia. Unfortunately, postoperative nausea and vomiting was a frequent disturbing adverse effect. (*Br. J. Anaesth.* 1997; **78**: 666–670).

**Key words**
Anaesthetic techniques, subarachnoid. Pain, postoperative. Anaesthetics local, bupivacaine. Analgesics opioid, morphine. Surgery, orthopaedic.

Continuous spinal anaesthesia and analgesia have been achieved effectively by administration of local anaesthetics for surgery and opioids for postoperative pain.[1–4] Opioids are generally given intrathecally for analgesia[3 5] either as a single bolus[3 5 6] or as a continuous infusion.[2 5] Treatment of postoperative nausea and vomiting (PONV) after intrathecal opioids has not yet been mastered.[7 8]

Recently, the usefulness of continuous administration of intrathecal bupivacaine for postoperative analgesia has been evaluated.[4 9] We showed that continuous infusion of bupivacaine 2 mg $h^{-1}$ produced adequate analgesia after hip and knee arthroplasty but the reappearance of spinal block and concomitant haemodynamic instability in some patients suggested that it was risky in terms of the benefits of this analgesia regimen.[4]

The synergism between local anaesthetics and opioids in extradural analgesia is a well established phenomenon.[10] This effect may be useful also in continuous intrathecal analgesia and thus the occurrence of adverse effects of both components should be reduced. Therefore, we have combined 0.25% bupivacaine and 0.002% morphine for low-dose continuous intrathecal infusion and evaluated its efficacy in the control of postoperative pain in comparison with infusion of bupivacaine alone.

## Patients and methods

The study was approved by the Ethics Committee of the hospital and informed consent was obtained from each patient. We studied 60 ASA I–III patients, aged 44–89 yr, undergoing elective hip or knee arthroplasty.

On the day of surgery, oral diazepam 5–15 mg was given as premedication. Subarachnoid puncture was performed in the midline at the L3–4 interspace, with the patient in the lateral position. A 28-gauge spinal catheter (CoSPAN Kendall, Basingstoke, UK) was inserted via a 22-gauge spinal needle. The catheters were advanced 3 cm past the needle tip into the subarachnoid space. Plain 0.5% bupivacaine 2 ml was injected via the catheter for induction of

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spinal anaesthesia. Patients undergoing knee arthroplasty were turned gently to the supine horizontal position and patients undergoing hip arthroplasty remained in the lateral recumbent position. Cephalad spread of analgesia was assessed by pinprick. After a period of 15 min, incremental doses of bupivacaine 0.5 ml were administered when necessary with the aim of reaching a spinal block level of T10.

A double-blind study design was used with patients allocated randomly to one of three groups, each comprising 20 patients. Patients received a coded solution for spinal infusion containing plain 0.5% bupivacaine 0.4 ml $h^{-1}$ (2 mg $h^{-1}$), plain 0.25% bupivacaine 0.4 ml $h^{-1}$ (1 mg $h^{-1}$) or 0.25% bupivacaine combined with morphine 20 μg $ml^{-1}$ (192 μg of morphine in 24 h). The infusion (JMS Syringe pump SP-100, JMS Company, Ltd, Hirosima, Japan) was started 60 min after induction of spinal anaesthesia if the level of spinal block was below T6. If not, the infusion was started after the sensory analgesia level had decreased below T6 and haemodynamic variables were stable. All patients had a urinary catheter during the study.

During operation, small doses of sedatives or fentanyl were given as required. I.v. fluids, including packed red cells, were given according to the clinical requirements of each patient. Arterial pressure and heart rate were recorded at 5-min intervals during surgery and at 10-min intervals in the post-anaesthesia care unit. ECG and peripheral oxygen saturation were monitored continuously. Patients were transferred to the ward 3–5 h after surgery when they were haemodynamically stable (changes in heart rate or arterial pressure ±15% compared with preoperative values).

For postoperative pain, paracetamol 1 g was given three times a day. If adequate analgesia was not achieved (at the operation site) oxycodone 0.14 mg $kg^{-1}$ i.m. was administered at request. Metoclopramide 10 mg i.v. was given for PONV when needed. Patients were interviewed by one of the investigators 3, 6, 12 and 24 h after the intrathecal infusion was started. Each interview included an assessment of the intensity of pain at rest and on movement of the operated leg using a visual analogue scale (VAS) (0–10). Cephalad extension of analgesia was assessed by pinprick and the degree of motor block (scale 0–3, 0=no block, 3=complete motor block) of the lower extremities was recorded using the criteria described by Bromage.[11] Heart rate, arterial pressure and the occurrence of nausea and vomiting were also recorded.

The spinal catheters were removed by one of the investigators on the first postoperative day. For removal, the patient was placed in the same flexed recumbent position as during the puncture.

### STATISTICAL ANALYSIS

Statistical analysis of patient data and single efficacy end-points (VAS values) was performed using one-way analysis of variance; Bonferroni corrections were used in pairwise comparisons. Frequency data were compared using the chi-square test. Motor and sensory block and doses of analgesics and antiemetic drugs needed were analysed with non-parametric Kruskal–Wallis one-way analysis of variance using the Bonferroni-corrected Mann–Whitney test for pairwise comparisons. $P<0.05$ was considered statistically significant.

## Results

The study was discontinued in five patients; two were excluded because of accidental disconnection of the hub of the catheter and one patient in the bupivacaine 2-mg $h^{-1}$ group and one patient in the bupivacaine–morphine group wanted the infusion interrupted because of disturbing reappearance of sensory (T6 and T9 dermatomes, respectively) and motor block. The patient in the bupivacaine

*Table 1* Patient characteristics (means (SD or range) or number)

| | Bupivacaine 2 mg $h^{-1}$ | Bupivacaine 1 mg $h^{-1}$ | Bupivacaine 1 mg $h^{-1}$—Morphine 8 μg $h^{-1}$ |
|---|---|---|---|
| No of patients | 18 | 18 | 19 |
| Age (yr) | 67 (44–88) | 66 (45–82) | 70 (48–84) |
| Weight (kg) | 78 (11) | 73 (11) | 71 (10) |
| Height (cm) | 169 (9) | 167 (8) | 165 (7) |
| Sex (F/M) | 10/8 | 11/7 | 15/4 |
| Surgery: hip/knee (No.) | 11/7 | 13/5 | 13/6 |
| Cephalad extension of spinal analgesia at 60 min (median (range)) | Th 7 (T2–T12) | Th 7 (T2–L1) | Th 8 (T3–L1) |

*Table 2* Postoperative 24-h requirements for oxycodone. $^{**}P=0.01$ (chi-square), bupivacaine 1 mg $h^{-1}$ compared with bupivacaine 2 mg $h^{-1}$ and bupivacaine–morphine; $^{\dagger}P<0.05$ (Kruskal–Wallis), bupivacaine 1 mg $h^{-1}$ compared with bupivacaine-morphine

| | Bupivacaine 2 mg $h^{-1}$ | Bupivacaine 1 mg $h^{-1}$ | Bupivacaine 1 mg $h^{-1}$—Morphine 8 μg $h^{-1}$ |
|---|---|---|---|
| No of patients | 18 | 18 | 19 |
| % Patients needing oxycodone | 39 | 78** | 31 |
| Oxycodone doses/group | 33 | 55† | 29 |
| Oxycodone doses/patient (mean, range) | 1.8 (0–7) | 3.0 (0–11) | 1.6 (0–13) |
| Time to first dose of oxycodone (min) (mean (SD)) | 214 (79) | 306 (211) | 451 (389) |

*Table 3* Data on postoperative patient interviews at fixed times during the 24-h follow-up. Patients estimated pain on a VAS (0–10) (mean (SD)). Cephalad extension of sensory block (dermatome) was assessed by pinprick and motor block by the Bromage score[11] (% of patients having motor block degree 2–3). There was more pain on movement than at rest: *$P<0.05$ (ANOVA), bupivacaine 1 mg h$^{-1}$ and bupivacaine–morphine compared with bupivacaine 2 mg h$^{-1}$, ††$P=0.01$ (Kruskal–Wallis), bupivacaine 2 mg h$^{-1}$ compared with the other groups; ‡$P<0.05$ (Kruskal–Wallis), bupivacaine–morphine compared with other groups; §$P<0.05$ (Kruskal–Wallis), bupivacaine 2 mg h$^{-1}$ compared with other groups

| | Bupivacaine 2 mg h$^{-1}$ | Bupivacaine 1 mg h$^{-1}$ | Bupivacaine 1 mg h$^{-1}$—morphine 8 µg h$^{-1}$ 3 h |
|---|---|---|---|
| VAS (rest) | 1.0 (1.9) | 1.3 (2.2) | 0.6 (1.3) |
| VAS (motion) | 1.3 (2.6) | 1.4 (2.5) | 0.6 (1.3) |
| Sensory block | L1 | L1 | L1 |
| Motor block (%) | 72% | 74% | 72% |
| 6 h | | | |
| VAS (rest) | 1.1 (1.9) | 1.4 (2.1) | 0.9 (1.2) |
| VAS (motion) | 1.4 (2.3) | 1.7 (2.5) | 1.3 (2.0) |
| Sensory block | L1 | L1 | L3‡ |
| Motor block (%) | 44% | 42% | 32% |
| 12 h | | | |
| VAS (rest) | 1.6 (2.5) | 2.4 (2.7) | 1.3 (1.7) |
| VAS (motion) | 2.1 (2.7) | 3.3 (3.1) | 2.2 (2.6) |
| Sensory block | T12§ | L4 | L3 |
| Motor block (%) | 33% | 11% | 32% |
| 24 h | | | |
| VAS (rest) | 1.5 (2.3) | 1.5 (1.8) | 1.0 (1.7) |
| VAS (motion) | 2.0 (2.6) | 3.5 (2.6)* | 2.4 (2.6)* |
| Sensory block | L2§ | 0 | 0 |
| Motor block (%) | 28%†† | 0 | 5% |

*Table 4* Postoperative nausea and vomiting. *$P<0.05$ (Kruskal–Wallis), bupivacaine 1 mg h$^{-1}$ compared with other groups

| | Bupivacaine 2 mg h$^{-1}$ | Bupivacaine 1 mg h$^{-1}$ | Bupivacaine 1 mg h$^{-1}$—morphine 8 µg h$^{-1}$ |
|---|---|---|---|
| No. of patients | 18 | 18 | 19 |
| Nausea (No.) | 3 | 7 | 7 |
| Vomiting (No.) | 2 | 5 | 3 |
| Requiring antiemetics (No.) | 1 | 5* | 0 |

2-mg h$^{-1}$ group also developed transient hypotension 10 h after surgery and required extra i.v. infusion of Ringer's acetate. One patient had an acute myocardial infarction and was therefore excluded from the study.

Data from the remaining 55 patients were analysed. Patient groups were comparable in age, weight, height, sex, arterial pressure and heart rate values obtained before operation, and type of surgery (table 1). Similarly, there were no differences in median cephalad dermatome level of sensory block 60 min after induction of spinal anaesthesia. Doses of sedatives, amount of intraoperative fluids and blood products did not differ between groups.

We found that 78% (14/18) of patients in the bupivacaine 1-mg h$^{-1}$ group needed supplementary opioid medication compared with 39% and 31% in the two other groups ($P=0.01$) during the 24-h postoperative period (table 2).

The number of supplementary oxycodone doses differed between groups ($P=0.04$), being higher in the bupivacaine 1-mg h$^{-1}$ group than in the other groups (table 2). Mean time from induction of anaesthesia to administration of i.m. opioid was comparable in all groups. VAS scores at 3, 6, 12 and 24 h at rest and on movement did not differ between groups. VAS scores were relatively low also during movement (table 3), and as a rule patients reported higher pain scores on movement than at rest (ns). At 24 h, patients who received either bupivacaine 1 mg h$^{-1}$ or bupivacaine–morphine experienced significantly more pain on movement of the operated leg than at rest compared with patients in the bupivacaine 2-mg h$^{-1}$ group ($P=0.03$) (table 3).

During the 24-h postoperative follow-up period, extension of sensory analgesia level and the intensity of motor block decreased in all groups. However, compared with the other groups, the bupivacaine 2-mg h$^{-1}$ group had significantly more extensive sensory block at 12 h ($P=0.02$) and at 24 h ($P=0.05$) than the other groups (table 3). Motor block was comparable in all groups at 3, 6 and 12 h. At 24 h after the start of infusion, partial motor block was observed in the bupivacaine 2-mg h$^{-1}$ group, and no motor block in the two other groups ($P=0.01$) (table 3).

On the ward all patients in the bupivacaine 2-mg h$^{-1}$ group, except the one mentioned above, were haemodynamically stable. There was no difference in the incidence of PONV between groups. Patients in the bupivacaine 1-mg h$^{-1}$ group were given more antiemetics than patients in the two other groups ($P=0.02$) (table 4). One patient in the bupivacaine 2-mg h$^{-1}$ group developed a minor decubitus on the heel of the operated extremity during the first week after surgery. This patient had second degree motor block 24 h after surgery, that is until the end of the intrathecal infusion. The skin healed with conservative therapy.

## Discussion

Our data indicated that continuous low-dose infusion of morphine 8 $\mu$g h$^{-1}$ combined with continuous infusion of bupivacaine 1 mg h$^{-1}$ provided as good postoperative analgesia as bupivacaine 2 mg h$^{-1}$ without opioid. This analgesic effect, as measured by requirements for supplementary opioids, was significantly better than the effect of bupivacaine 1 mg h$^{-1}$ alone. In addition to analgesia via spinal cord opioid receptors, intrathecal morphine suppresses selectively ascending A-delta and C-fibre activity evoked by stimulation of primary nociceptive afferents.[12] In animal models it has been shown that spinally administered morphine potentiates the analgesic effects of bupivacaine.[13] This concept has been used successfully in extradural analgesia for many years.[14,15] It is suggested that bupivacaine induces conformational change in the spinal opioid receptor thus facilitating synergism.[13] This synergistic effect has been demonstrated previously using single bolus doses in the clinical setting.[16]

In addition to good analgesia, the bupivacaine–morphine combination caused less motor block than the higher dose of bupivacaine alone. This might be clinically important even in patients who are not allowed to move in the first 24 h after surgery, because patients are encouraged to exercise their legs as early as possible in order to maintain good perfusion of the extremities, even during bed rest. The bed sore on the heel of one of our patient may be blamed on postoperative analgesia. Therefore, when higher doses of continuous intrathecal local anaesthetics are used it is important that the patient's position must be changed during the postoperative period if they are not able to move their legs voluntarily.

The use of spinal morphine, especially in higher doses, is associated with adverse effects such as respiratory depression, urinary retention, pruritus, and nausea and vomiting.[17] Higher peak concentrations of opioids observed after single boluses may increase the incidence and severity of side effects.[18] In our study we did not notice any difference in the incidence of nausea and vomiting between the groups, perhaps because the dose of morphine was relatively small. Interestingly, requirements for antiemetic medication were highest in the bupivacaine 1-mg h$^{-1}$ group. One explanation might be that patients in this group needed more systemically administered supplementary opioids which possibly induced greater intensity of nausea and therefore a greater demand for antiemetics.

Intrathecally administered plain bupivacaine is unpredictable regarding the final cephalad spread of the block.[19] In our study only one patient (in the bupivacaine 2-mg h$^{-1}$ group) suffered transient hypotension on the ward. This was related to the reappearance of the spinal block to T6. Also, in our previous study with intrathecal infusion of plain bupivacaine, reappearance of spinal block occurred relatively late during the first postoperative day.[4] Previously we have demonstrated changes in the level of bupivacaine spinal anaesthesia by changing the patient's posture 80–115 min after induction of anaesthesia.[20] Such a sudden change is probably caused by bulk displacement of CSF and movement of local anaesthetic which has not yet been bound or absorbed. On the other hand, the slowly progressing extension of the block on the ward, with patients in the horizontal position, resembles the slower diffusional type of drug distribution.

Regional anaesthetic and analgesic techniques are becoming popular for postoperative analgesia.[21] Extradural opioids are frequently combined with local anaesthetics for postoperative extradural analgesia because of their synergistic effects. For instance, combinations of morphine and bupivacaine,[22] fentanyl and bupivacaine[23] or sufentanil and bupivacaine[24] for extradural postoperative analgesia have been found to be superior to bupivacaine alone. Most importantly, the synergistic combination of an opioid and bupivacaine appears to be effective for pain during movement.[22] Also, in this study enhanced intrathecal analgesia tended to be more pronounced with movement but was also present at rest.

It should be emphasized that the intensity of pain experienced by our patients remained low also at movement and therefore the tests we used may not be sensitive enough to detect a significant additive or synergistic analgesic effect of drug combinations.[25]

Continuous spinal anaesthesia with local anaesthetics produces profound intraoperative analgesia and motor block and the duration of analgesia can be adjusted to the duration of surgery. In spite of technical problems,[8,26] when a spinal microcatheter has been placed for intraoperative analgesia, it may be used after operation also. We have demonstrated that the combination of a low dose of morphine (8 $\mu$g h$^{-1}$) and bupivacaine (1 mg h$^{-1}$) produced as good postoperative analgesia as twice the dose (2 mg h$^{-1}$) of bupivacaine alone, but with less motor block.

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# Hyaluronidase and peribulbar block

G. A DEMPSEY, P. J. BARRETT AND I. J. KIRBY

## Summary

We have assessed the effect of two concentrations of hyaluronidase on the quality of peribulbar block, using a low volume, single injection technique. We studied 200 patients undergoing elective intraocular surgery, allocated randomly to one of three groups. Group 1 (*n*=50) received peribulbar block with 5 ml of a 1:1 mixture of 0.5% plain bupivacaine and 2% plain lignocaine. Group 2 (*n*=75) received this solution supplemented with hyaluronidase 50 iu ml$^{-1}$. Group 3 (*n*=75) received the same solution supplemented with hyaluronidase 300 iu ml$^{-1}$. Lack of ocular motility was considered to be the only objective sign of successful block and movement of each rectus muscle was scored at 1-, 5- and 10-min intervals. If the block was successful at 5 min, the 10-min score was omitted. If the block was unsuccessful at 5 min, a second injection of 2% lignocaine 3 ml was given and additional assessments performed at 5-min intervals. At 1 min, ocular motility scores were significantly lower in group 3 compared with the control group ($P<0.05$). The incidence of satisfactory block at 5 min was increased in both groups given hyaluronidase (group 2, $P<0.05$; group 3, $P<0.001$). There were no significant differences between groups 2 and 3 with respect to quality of block at 5 min. Hyaluronidase in both concentrations improved the quality of peribulbar block at 5 min, and when used in a concentration of 300 iu ml$^{-1}$, also improved the speed of onset of block. (*Br. J. Anaesth.* 1997; **78**: 671–674).

**Key words**
Anaesthetic techniques, regional, peribulbar. Surgery, ophthalmic Enzymes, hyaluronidase.

Peribulbar block provides good quality local anaesthesia for intraocular surgery, combining low morbidity with high efficacy.[1] Hyaluronidase is thought to promote the spread of local anaesthetic solutions by hydrolysing glycosidic bonds within the hyaluronic acid which forms the interstitial barrier.[2] Its efficacy has been proved when used for retrobulbar block.[3 4] However, its advantage in peribulbar block is less clear, with some studies claiming no beneficial effect[5 6] and others reporting improved quality of block.[7 8] Those studies claiming no beneficial effect have used varying concentrations of hyaluronidase, up to 150 iu ml$^{-1}$, and studied relatively few patients. More recently, pH-adjusted solutions containing hyaluronidase have been used to some effect.[9]

We postulated that the uncertainty relating to the effect of hyaluronidase on peribulbar block may result in part from insufficient numbers of patients studied and also from the use of inadequate concentrations. Therefore, we have performed a large, randomized, controlled study to assess the effect of two concentrations of hyaluronidase on the quality of peribulbar block.

## Patients and methods

After approval from the local Ethics Committee and informed consent, we studied 200 unpremedicated patients, ASA I, II or III, undergoing elective intraocular surgery under local anaesthesia. Patients were allocated randomly to one of three groups: group 1 (*n*=50) received peribulbar block with 5 ml of a 1:1 mixture of 0.5% plain bupivacaine and 2% plain lignocaine; this group served as a control. Group 2 (*n*=75) received the same volume of solution supplemented with hyaluronidase 50 iu ml$^{-1}$. Group 3 (*n*=75) received the same solution supplemented with hyaluronidase 300 iu ml$^{-1}$.

Before the block, a vein was cannulated and monitoring of heart rate, oxygen saturation and non-invasive arterial pressure was commenced in all patients. Topical anaesthesia to the infraorbital skin was provided by EMLA cream applied at least 1 h before surgery, and to the conjunctiva by 0.4% oxybuprocaine drops applied immediately before performing the block.

All blocks were performed by the same investigator using a low volume (5 ml), single transcutaneous inferolateral injection technique, and a standard 25-mm, 23-gauge needle, as described by Apel and Woodward.[10] With the gaze fixed straight ahead in the primary position, the injection site was identified at the junction of the lateral one-third and medial two-thirds of the inferior orbital rim. The direction of needle insertion was slightly medial and cephalad, with the tip of the needle being elevated towards the end of injection. Immediately after injection, a McIntyre weight (mercury-filled bag)

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was applied to the closed eye to promote spread of local anaesthetic and softening of the globe. Reduction of ocular motility was considered to be the only reliably reproducible sign of successful block; movement of the superior, inferior, medial and lateral recti were scored by an observer blinded to the solution used, in a manner similar to that described by Nicoll and colleagues.[4]

Movements were scored as: normal=2, reduced=1 and akinesia=0, giving a maximum aggregate score for the four muscles of 8. Ocular motility was assessed at 1-, 5- and 10-min intervals and a score of 4 or less, from reduced movements in all directions, was taken to indicate successful block. If a successful block was achieved at 5 min, the 10-min score was omitted. If however, the block was unsuccessful at 5 min, supplementary injection of 2% plain lignocaine 3 ml was administered, in the manner described earlier, with additional assessments performed at 5-min intervals. The total volume of local anaesthetic required to produce successful block was recorded. Increased intraocular pressure was assessed by experienced palpation only: it was noted whether or not the eye felt tense.

### STATISTICAL ANALYSIS

Patient data were analysed using analysis of variance (ANOVA), while ocular motility scores and total volume of local anaesthetic required were compared using chi-square tests. Clinical detection of increased intraocular pressure in the three groups was compared using Fisher's exact test.

## Results

There were no significant differences between the three groups in age, sex or ASA status (table 1).

Ocular motility scores at 1 min for group 3 were significantly lower than control values (group 1), with 39 (52%) patients achieving a score of $\leqslant 4$. There were no significant differences at 1 min between groups 1 and 2 or groups 2 and 3 (table 2).

*Table 1* Patient characteristics in the three groups (mean (range) or number). H=Hyaluronidose

| | Group 1 (control) | Group 2 (H 50 iu Ml$^{-1}$) | Group 3 (H 300 iu Ml$^{-1}$) |
|---|---|---|---|
| Age (yr) | 76 (47–93) | 75 (58–93) | 76 (46–95) |
| Sex (M/F) | 17/33 | 21/54 | 28/47 |
| ASA Status | | | |
| I/II/III | 11/16/23 | 12/34/29 | 12/27/36 |

*Table 2* Numbers (%) of patients in each group with an ocular motility score at 1 min of less than or more than 4. $^{*}P<0.05$ compared with control (chi squared). H=Hyaluronidose

| | Score $\leqslant 4$ (%) | Score $>4$ (%) |
|---|---|---|
| Group 1 | | |
| Control ($n$=50) | 15 (30) | 35 (70) |
| Group 2 | | |
| H 50 iu ml$^{-1}$ ($n$=75) | 29 (39) | 46 (61) |
| Group 3 | | |
| H 300 iu ml$^{-1}$ ($n$=75) | 39 (52)* | 36 (48) |

*Table 3* Numbers of patients achieving successful block at 5 min (%). $^{*}P<0.05$, $^{**}P<0.001$ compared with control (chi squared). H=Hyaluronidase

| | Successful block (%) | Unsuccessful block (%) |
|---|---|---|
| Group 1 | | |
| Control ($n$=50) | 33 (66) | 17 (34) |
| Group 2 | | |
| H 50 iu ml$^{-1}$ ($n$=75) | 63 (84)* | 12 (16) |
| Group 3 | | |
| H 300 iu ml$^{-1}$ ($n$=75) | 68 (91)*** | 7 (9) |

*Table 4* Numbers of patients achieving complete akinesia by 10 min (%). $^{*}P<0.05$, $^{**}P<0.001$ compared with control (Chi squared). H=Hyaluronidase

| | Complete akinesia (%) |
|---|---|
| Group 1 | |
| Control ($n$=50) | 9 (18) |
| Group 2 | |
| H 50 iu ml$^{-1}$ ($n$=75) | 26 (35)* |
| Group 3 | |
| H 300 iu ml$^{-1}$ ($n$=75) | 30 (40)*** |

At 5 min, the incidence of successful blocks was significantly greater in both group 2 ($P<0.05$) and group 3 ($P<0.001$) compared with the control. There were no significant differences between groups 2 and 3 at this time for both achieving an ocular motility score of $\leqslant 4$ (table 3) and achieving complete akinesia (table 4).

By 5 min, 164 patients from the three groups had achieved successful block and were not assessed further. Of the remaining 36 patients, 34 had achieved successful block by 10 min after a second injection. All but two of the 200 patients had achieved successful block by 10 min; both of these patients were from group 3 and required a third injection (total volume of local anaesthetic 11 ml) to achieve successful block. No patient proceeding to surgery experienced any intraoperative discomfort.

Four patients in group 1 had clinical evidence on palpation of a sustained increase in intraocular pressure (IOP). In one case this necessitated cancellation of surgery. In another patient, i.v. acetazolamide was required and in the two other patients, ocular compression for 20 min before surgery was necessary. None of the four patients noted to have a "tense" eye on palpation had received a volume of injectate greater than 5 ml, as all had achieved ocular motility scores of 4 or less by 5 min.

The two patients with the most marked increases

*Table 5* Numbers (%) of patients with clinical evidence of increased intraocular pressure (IOP). $^{***}P<0.001$ compared with control (Fisher's exact test). H=Hyaluronidase

| | IOP satisfactory | "Tense" eye |
|---|---|---|
| Group 1 | | |
| Control ($n$=50) | 46 (92) | 4 (8) |
| Group 2 | | |
| H 50 iu ml$^{-1}$ ($n$=75) | 75 (100)*** | 0 (0) |
| Group 3 | | |
| H 300 iu ml$^{-1}$ ($n$=75) | 75 (100)*** | 0 (0) |

in IOP were brought to our attention by the ophthalmic surgeon who was unaware of the local anaesthetic solution used. The remaining two patients were noted to have "tense" eyes by one of the authors, who may have been aware of the solution used. Comparison of the number of patients in each group with a tense eye, using Fisher's exact test, showed a highly significant difference ($P<0.001$) between the three groups (table 5).

As the risks involved in undertaking intraocular surgery in patients with a high IOP are significant, we felt that we were no longer justified in recruiting to group 1 and only 50 patients were studied.

## Discussion

We have demonstrated a beneficial effect of hyaluronidase 300 iu ml$^{-1}$ combined with 0.5% bupivacaine and 2% lignocaine in improving the speed of onset of peribulbar block compared with local anaesthetic solutions alone. Hyaluronidase in concentrations of 300 iu ml$^{-1}$ and 50 iu ml$^{-1}$ also improved the quality of peribulbar block at 5 min compared with control, reducing the need for supplementary injection. We were unable to show any significant difference between the two concentrations of hyaluronidase with respect to quality of block at 5 min.

A study by Roberts, Macleod and Hollands suggested that the beneficial effects of hyaluronidase appeared only when local anaesthetic solutions were alkalinized to allow improved enzymatic action.[9] Our findings do not concur with these results in that we found hyaluronidase to be effective in improving the quality of block without pH adjustment. This may partly result from the different concentrations of hyaluronidase used in the two studies (10 iu ml$^{-1}$ *vs* 50/300 iu ml$^{-1}$), differences in technique (two injection peribulbar technique *vs* single injection peribulbar block) and time of assessment (only at 30 min compared with 1, 5 and 10 min in our study). There were also differences in study design with the former using five different groups and studying only 100 patients.

In addition, our own observations showed that the use of hyaluronidase itself may alter the pH of a local anaesthetic because of the presence of phosphate buffers within the preparation, so that a 1:1 mixture of 0.5% plain bupivacaine and 2% plain lignocaine has a pH of 4.9, the same solution with hyaluronidase 50 iu ml$^{-1}$ has a pH of 5.0, while a solution with hyaluronidase 300 iu ml$^{-1}$ has a pH of 5.6. It is well recognized that local anaesthetics exist in both the uncharged and charged cationic forms within the body and that the ratio between the two varies with the pH of the surrounding tissues. It is believed that local anaesthetic molecules penetrate nerve membranes more rapidly in their uncharged form,[11] with the ionized form being the active structure.[12] For both lignocaine and bupivacaine, as pH decreases, there is an increase in the cationic form. Conversely, as pH increases, more of the drug exists in the free base form, allowing the drug to penetrate the nerve fibre more rapidly. Several authors have found alkalinizing local anaesthetic solutions to be effective for both peribulbar block[13] and other blocks.[14] It may be that the efficacy of hyaluronidase in improving onset of block is at least partly a result of its ability to increase the pH of local anaesthetic solutions.

It has also been postulated that because of its effects on absorption, hyaluronidase may lead to higher plasma concentrations of local anaesthetic and reduce the duration of action of block.[15] A recent study showed that addition of hyaluronidase to local anaesthetic solutions hastened the absorption of both lignocaine and bupivacaine but did not increase the maximum plasma concentration achieved.[16] Although we did not measure plasma concentrations of local anaesthetic, toxicity with this technique would not be expected because of the small amount of drug used. Duration of nerve block was sufficient to complete surgery in all patients.

Of additional interest in this study was the sustained increase in IOP in four patients in the control group, which occurred despite the use of a low volume of injectate (5 ml). We felt that this was so significant that we could no longer justify further recruitment to this group. There is only one previous report which suggested an association between peribulbar block without hyaluronidase and sustained increases in IOP.[17] The underlying aetiology may be related to incomplete dispersal of local anaesthetic solution within the periocular compartment. However, all patients who had increases in IOP appeared clinically to have small orbits with short axial lengths (all ≤22 mm). This observation may warrant further investigation.

Each time a needle is introduced into the orbit, there is a small but definite risk of complication. Successful block from a single injection is therefore desirable. Our study has shown that this is most likely to be achieved when hyaluronidase is added to the solution. Because of its beneficial effects on speed of onset, ease of administration and lack of significant toxicity or adverse effect on local anaesthetic absorption, we would advocate the use of hyaluronidase in a concentration of 300 iu ml$^{-1}$.

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*British Journal of Anaesthesia* 1997; 78: 675–677

# Intraperitoneal lignocaine for pain relief after total abdominal hysterectomy

K. M. WILLIAMSON, B. R. COTTON AND G. SMITH

## Summary

In this preliminary randomized study, we have measured pain scores at rest and on movement, 24 and 48 h after operation in 19 control patients, who received 50 ml of saline i.p., and in 20 test patients, in whom 50 ml of saline solution containing lignocaine 200 mg and adrenaline 1:500 000 were instilled into the peritoneal cavity after total abdominal hysterectomy. We found that there was no difference in linear analogue scores for nausea, pain on movement or morphine consumption after operation between the two groups, but pain scores at rest were significantly lower in the lignocaine group at 24 and 48 h compared with the saline group. In the lignocaine group, blood sampling over a 3-h period revealed a mean maximum serum concentration of 0.4 $\mu$g ml$^{-1}$ at 3 h and a highest concentration in any patient of 0.87 $\mu$g ml$^{-1}$. (*Br J. Anaesth.* 1997; **78**: 675–677).

**Key words**
Surgery, gynaecological. Anaesthetics local, lignocaine. Pain, postoperative.

Recently, there has been interest in the instillation of local anaesthetic solutions into the peritoneal cavity for treatment of pain after abdominal surgery. This technique has been described as producing effective analgesia after laparoscopic cholecystectomy by some workers[1–2] but not by others.[3] After gynaecological laparoscopy, there is stronger evidence for effective analgesia.[4–7] Serum concentrations of local anaesthetics have been measured after i.p. administration of lignocaine and bupivacaine during gynaecological laparoscopy and the authors concluded that the use of a plain solution of lignocaine led to relatively high but safe serum concentrations of the drug with a dose of 400 mg. The addition of adrenaline was shown to produce a substantial reduction in the maximum serum concentrations attained.[8]

We were interested to see if i.p. instillation of local anaesthetic produced effective analgesia after total abdominal hysterectomy. Because of the greater degree of trauma after hysterectomy than after laparoscopy, we were concerned that the rate of absorption of local anaesthetic might be faster after hysterectomy. Consequently, we devised a study to assess serum concentrations of lignocaine after instillation of a relatively small dose (200 mg) of lignocaine into the peritoneal cavity and, at the same time, examine the effect on postoperative analgesia to serve as a guide to a subsequent study designed to assess the analgesic efficacy of larger doses of local anaesthetic solutions.

## Patients and methods

After obtaining approval from the Leicestershire Ethics Committee and written informed patient consent, we studied 40 patients undergoing total abdominal hysterectomy. All patients were aged 20–60 yr, ASA grade I or II, not undergoing surgery for malignancy and were scheduled for surgery undertaken via a standard Pfannenstiel incision. Patients were excluded if they had cardiac or vascular disease, hepatic disease, allergy to local anaesthetic agents or any contraindications to local anaesthesia.

Anaesthesia was standardized and comprised premedication with temazepam 10 mg, induction with propofol 150–200 mg, intubation of the trachea and controlled ventilation of the lungs using 1.5–2.0% enflurane and 66% nitrous oxide in oxygen. Vecuronium was given as required to produce neuromuscular block and a standard dose of morphine 10 mg (combined with prochlorperazine 12.5 mg) was given shortly after induction of anaesthesia to provide analgesia in the immediate postoperative period. After induction of anaesthesia, a second cannula was inserted into the contralateral antecubital fossa from the arm in which the i.v. infusion was sited and 10-ml samples of venous blood were obtained before and at 1, 3, 5, 10, 15, 20, 30, 60, 120 and 180 min after instillation of local anaesthetic into the peritoneal cavity. After administration of morphine, patients were allocated randomly using sealed envelopes and random numbers generated by computer to receive either local anaesthetic solution or an equal volume of saline solution. The local anaesthetic solution comprised 50 ml of 0.4% lignocaine with adrenaline (1:500 000 dilution) prepared by adding 30 ml of saline to 20 ml of 1% lignocaine containing adrenaline 1:200 000.

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Total abdominal hysterectomy was carried out using a standard technique by one of four surgeons, the majority being performed by a single surgeon. The peritoneum over the vault of the vagina was not closed and the local anaesthetic or saline solution was instilled into the pelvic cavity only after haemostasis had been secured, all packs removed from the peritoneal cavity and the patient placed in the supine horizontal position.

After operation, patients were provided with patient-controlled analgesia equipment (Abbott PCA II; morphine 1-mg boluses with 8-min lock-out), the use of which had been explained in detail at the preoperative assessment. This technique is used routinely and supervised by the sister in the acute pain service at Leicester Royal Infirmary. The patient and pain sister, who acted as an observer, the recovery room staff, surgical staff and the nursing staff on the ward were blinded to the nature of the solution administered into the peritoneal cavity. In our hospital, the pain sister is allowed to give bolus doses of morphine up to 5 mg i.v. in the recovery room in order to provide optimal analgesia immediately after recovery.

In the postoperative period, the patient completed linear analogue pain scores, at 24 and 48 h, for pain at rest and during a standardized movement (sitting upright from the supine horizontal position). In addition, she completed linear analogue scores for nausea and sedation.[8]

Serum concentrations of lignocaine were measured using high pressure liquid chromatography and ultraviolet detection. The intra-assay coefficient of variation was 3.6% and the inter-assay coefficient of variation was 4.2%. The limit of detection was 0.04 μg $ml^{-1}$.

Data were analysed using SPSS version 6.0 for Windows running on an IBM compatible PC and serum concentrations of lignocaine were plotted using Graphpad Prism version 2.0. Data were subjected first to Komolgorov–Smirnov goodness of fit tests for normality of distribution. All data were found to be distributed normally and were therefore compared using the Student's *t* test. $P<0.05$ was taken as significant. Because of concern about the normality of distribution of linear analogue scores, data were analysed also by Mann–Whitney *U* tests.

## Results

Data from one patient in the saline group were rejected because of failure of standardization of the anaesthetic technique. Thus we have compared data from 19 patients in the saline group with 20 in the lignocaine group. The two groups were comparable in age and duration of anaesthesia (table 1). Cumulative morphine consumption (total given in the intraoperative period, in the recovery room and by PCA) in the first 24 and 48 h was the same in both groups and the mean number of injections of prochlorperazine to control vomiting was the same also in both groups. There was no difference between the two groups in the bolus dose of morphine given by the pain sister in the recovery room. In the saline group, there was a total of 11 episodes of vomiting (number of individual retchings or vomits) in seven patients and in the lignocaine group a total of nine episodes of vomiting in six patients, all within the first 24 h.

*Table 1* Patient characteristics and postoperative data (mean (SEM) or range)

| | Saline ($n$=19) | Significance | Lignocaine ($n$=20) |
|---|---|---|---|
| Age (yr) | 43.2 (30–58) | ns | 39.6 (28–59) |
| Weight (kg) | 63.8 (2.3) | ns | 63.1 (1.9) |
| Duration of anaesthesia (min) | 60.2 (2.9) | ns | 55.5 (2.7) |
| Morphine consumption (mg) | | | |
| 0–24 h | 59.8 (3.6) | ns | 59.5 (4.3) |
| 0–48 h | 89.4 (5.4) | ns | 75.8 (6.9) |
| Dose of prochlorperazine (mg) | | | |
| 0–24 h | 11.3 (2.3) | ns | 15.6 (2.9) |
| Episodes of vomiting | | | |
| 0–24 h | 11 ($n$=7) | ns | 9 ($n$=6) |
| 24–48 h | 0 | | 0 |
| Pain scores (mm) | | | |
| At 24 h rest | 39.4 (4.7) | <0.05 | 26.0 (4.1) |
| At 24 h movement | 47 0 (6.0) | ns | 42.0 (4.6) |
| At 48 h rest | 23.2 (3.9) | <0.05 | 11.5 (2.7) |
| At 48 h movement | 33.6 (4.1) | ns | 23 5 (3.6) |

After operation, there was a small but significant difference in linear analogue pain scores both at 24 and 48 h for patients at rest; the lignocaine group reported significantly less pain than the saline group ($P<0.05$ using Student's *t* tests and also the Mann–Whitney *U* test). Although there was also less pain reported on movement in the lignocaine group, this was not significantly different from that in the saline group. There were no significant differences between the two groups in linear analogue scores for nausea or sedation (data not shown).

Lignocaine was absorbed rapidly from the peritoneal cavity; serum concentrations reached a plateau by approximately 5 min after instillation into the pelvic cavity. Thereafter, plasma lignocaine concentration tended to increase very slowly and to a very slight extent for the duration of sampling over 3 h (fig. 1). The final mean maximum concentration achieved at 3 h was approximately 0.4 μg $ml^{-1}$. The highest concentration observed at any time in any patient was 0.87 μg $ml^{-1}$.

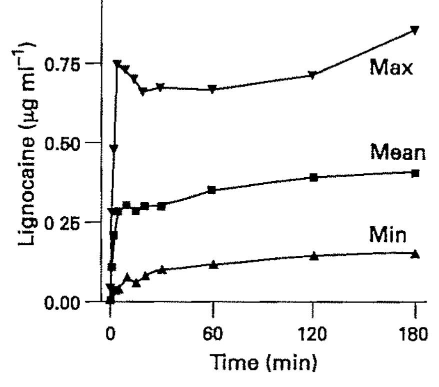

*Figure 1* Serum concentrations of lignocaine after instillation of a dose of 200 mg with adrenaline 1:500 000 into the pelvic cavity after hysterectomy. Data shown as mean values with minima and maxima ($n$=20).

## Discussion

We have found that instillation of a relatively small dose of lignocaine (200 mg) into the pelvic cavity before closure of a Pfannenstiel incision after total abdominal hysterectomy was associated with lower pain scores at rest, at 24 h and at 48 h after operation compared with a control group given saline; however, only data for pain at rest were statistically significant. In every other respect, the two groups of patients behaved in a similar manner, with the same degree of postoperative emesis, same requirements for antiemetics and similar consumptions of morphine by PCA over the 48-h period after operation. There was no morbidity associated with instillation of solutions into the peritoneal cavity and there was no morbidity or mortality in the patients examined in this study.

We found that lignocaine was absorbed relatively rapidly from the peritoneal cavity reaching approximately 0.25 $\mu$g ml$^{-1}$ by 5 min, but subsequently there was a slow gradual increase up to approximately 0.4 $\mu$g ml$^{-1}$ by 3 h after instillation.

Narchi and colleagues [8] found that, after gynaecological laparoscopy, the rate of absorption of lignocaine from the peritoneal cavity was relatively slow; the time to maximum concentration ($tC_P$max) was reached at 29 min with plain lignocaine 400 mg, at 58 min using lignocaine 400 mg with adrenaline 1:320 000 and at 72 min with lignocaine 400 mg and adrenaline 1:800 000. In both Narchi's study and ours, the maximum concentration of lignocaine attained ($C_P$max) was relatively low. Narchi and colleagues found a $C_P$max value of 4.3 $\mu$g ml$^{-1}$ with plain lignocaine 400 mg, 2.3 $\mu$g ml$^{-1}$ with lignocaine 400 mg and adrenaline 1:320 000, and 1.89 $\mu$g ml$^{-1}$ using lignocaine 400 mg with adrenaline 1:800 000.

We used half the dose of lignocaine that Narchi and colleagues used. Our data suggest that if we had used lignocaine 400 mg with adrenaline, we would have found a $C_P$max value of 0.8 $\mu$g ml$^{-1}$ which is one-third of the $C_P$max found in that study; this suggests that the rate of absorption of lignocaine was slower after hysterectomy than after gynaecological laparoscopy.

The serum concentration of lignocaine at which toxic symptoms begin to occur is approximately 3 $\mu$g ml$^{-1}$ in the unmedicated subject but the threshold increases in patients during anaesthesia.[9] Thus our data suggest that a dose of lignocaine 400 mg would be extremely unlikely to result in toxicity when given into the pelvic cavity after abdominal hysterectomy.

In summary, we have found that administration of lignocaine 200 mg into the peritoneal cavity after total abdominal hysterectomy was associated with low serum concentrations of lignocaine and that it should be possible to administer a larger dose of 400 mg without fear of approaching toxic concentrations. Furthermore, we have obtained some evidence that lignocaine 200 mg was associated with a measurable analgesic effect, although of modest clinical magnitude. Thus this preliminary study suggests that the technique is safe, and that it is worthwhile examining the use of larger doses of lignocaine and also bupivacaine for analgesia after total abdominal hysterectomy.

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# Pre-anaesthetic assessment of coagulation abnormalities in obstetric patients: usefulness, timing and clinical implications

L. SIMON, T. M. SANTI, P. SACQUIN AND J. HAMZA

## Summary

The usefulness and optimal timing of laboratory coagulation tests before obstetric extradural analgesia are controversial. Moreover, the significance of mild coagulation abnormalities during pregnancy remains unclear. We have assessed the reliability of coagulation tests performed several weeks before delivery as predictors of coagulation abnormalities during labour. Platelet count, plasma fibrinogen concentration, prothrombin time (PT) and activated partial thromboplastin time (aPTT) were sampled in 797 women during the ninth month of pregnancy and checked during labour. Platelet count was less than $100 \times 10^9$ litre$^{-1}$ for 11 women during labour. Only three had been detected by the first sample. Platelet count less than $100 \times 10^9$ litre$^{-1}$ or fibrinogen concentration less than 2.9 g litre$^{-1}$ during labour were associated with an increase in the incidence of postpartum haemorrhage (odds ratio=19.7). We conclude that a platelet count several weeks before delivery was not reliable in predicting thrombocytopenia during labour and that women with mild coagulation abnormalities in early labour may need special attention regarding the risk of postpartum haemorrhage. (*Br. J. Anaesth.* 1997; **78**: 678–683).

**Key words**
Anaesthesia, obstetric. Anaesthetic techniques, extradural. Blood, haemostasis. Blood, coagulation.

In a recent survey of 435 French obstetric units,[1] most anaesthetists advocated laboratory coagulation tests before extradural analgesia for labour. In this study, coagulation tests were performed during the ninth month of pregnancy in 74% of obstetric units surveyed. They included prothrombin time (PT), activated partial thromboplastin time (aPTT) and platelet count in almost all cases. Although haemostasis disorders seem to increase the risk of extradural haematoma,[2] the usefulness of laboratory coagulation screening tests is still debatable.[3] However, platelet count can decrease during pregnancy[4] and the incidence of thrombocytopenia has been shown to increase during labour.[5] The significance of this thrombocytopenia remains unclear and determination of a safe lower platelet count limit before performing extradural analgesia is still controversial. Many anaesthetists avoid extradural analgesia if platelet count is less than $100 \times 10^9$ litre$^{-1}$,[6–8] but this limit has no supporting data.[9] Another difficulty in coagulation assessment is the choice of when to perform it. Haemostasis disorders can appear late in pregnancy. Therefore, a medical history, physical examination and laboratory testing may be inadequate in detecting these haemostasis disorders if they are performed too early.[10] In addition, no relationship between mild coagulation abnormalities during pregnancy and haemorrhagic complications during extradural analgesia[11] or delivery[12] have yet been established.

Therefore, we designed a prospective study to evaluate the accuracy of laboratory coagulation tests performed during the ninth month of pregnancy to predict coagulation abnormalities during labour. We also examined the incidence of these coagulation abnormalities during labour and their relationship with post-partum haemorrhage (PPH).

## Patients and methods

This prospective surveillance study was performed between 1 June 1995 and 31 December 1995. During this period, we studied all women with a singleton pregnancy who came into the labour ward for delivery. As the study was an anonymous survey of haematological and clinical variables, hospital Ethics Committee approval was not required. Inclusion criteria were: pre-anaesthetic clinical assessment during the ninth month of pregnancy, physical status ASA I or II, and term >36 and <42 weeks at the time of delivery. We excluded all women with a medical history known to be associated with haemostasis disorders, such as von Willebrand disease, diabetes mellitus, idiopathic thrombocytopenic purpura or lupus erythematosus. We also excluded women receiving anticoagulant therapy and parturients admitted for elective Caesarean section.

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### STUDY DESIGN

The first blood sample (BS 1) for laboratory coagulation tests was obtained in each parturient during the ninth month of pregnancy, usually just after pre-anaesthetic clinical assessment. Platelet count, PT, aPTT and plasma fibrinogen concentration were determined in each sample. When the women entered the labour ward for delivery, a second blood sample (BS 2) was obtained for the same tests via a 16-gauge i.v. cannula just before the start of a basal infusion of Ringer's lactate solution. Age, parity, medical and obstetric history, and gestational age (GA) were obtained by an anaesthetist, who enquired again of any previous history of bleeding. He also noted on the anaesthetic chart all recent antepartum medical complications such as pre-eclampsia, sepsis or placenta praevia. Each abnormal coagulation test result was checked systematically in a new sample. Moreover, thrombocytopenia (platelet count $<100\times10^9$ litre$^{-1}$) was confirmed by examination of the stained peripheral blood film to exclude platelet clumping. BS 2 was always available before the decision to proceed with extradural analgesia. If indicated, extradural analgesia was provided for labour in each parturient whose platelet count was more than $100\times10^9$ litre$^{-1}$ at BS 2.

When the women left the labour ward, the route of delivery (vaginal delivery or Caesarean section) and the occurrence of PPH were noted. Only significant haemorrhages were considered. These were defined as clinically severe bleeding requiring volume expansion and manual uterine exploration, associated with either blood transfusion or a significant decrease ($\geqslant2$ g dl$^{-1}$) in haemoglobin concentration, or both, within 24 h post-partum.

We compared for each parturient the results of BS 1 and BS 2, and we calculated the changes in platelet count (%) and fibrinogen concentration (g litre$^{-1}$) between the two periods. Then we examined mean (SD) platelet count and fibrinogen concentration in BS 2. Values less than the lower threshold of the corresponding 95% confidence limits (value $\leqslant$mean value $-1.96$ SD) for one or both variables, or with a PT <70% or an aPTT >40 s (normal 30 s) were classified as "coagulation abnormalities". We compared the incidence of severe PPH in this group and in the other women.

### STATISTICAL ANALYSIS

Results are expressed as mean (SD). For quantitative data, statistical analysis was performed using analysis of variance for repeated measures. When overall differences were detected, individual comparisons between groups were performed by Student's *t* test with Bonferroni's correction. Fisher's exact test was used to compare nominal data.

## Results

We studied 835 parturients: 797 were included in the results and statistical analyses, and 38 were excluded. The characteristics of these 38 patients in the labour ward are shown in table 1. Mean delay between BS 1 and BS 2 was 17 (9) days (always less than 30 days).

*Table 1* Information on 38 women excluded from the study. Reasons for exclusion are indicated

| | |
|---|---|
| *n* | 38 |
| Age (yr) (mean (range)) | 30.9 (24–43) |
| Gestational age (weeks) (mean (SD)) | 38.2 (2.4) |
| Reasons for exclusion in labour ward | |
| Placenta praevia | 8 |
| Placenta abruptio | 2 |
| Fever >38.5°C ± sepsis syndrome | 6 |
| BS 2 not available | 10 |
| Low molecular weight heparin therapy | 3 |
| Hypertension and/or pre-eclampsia | 9 |

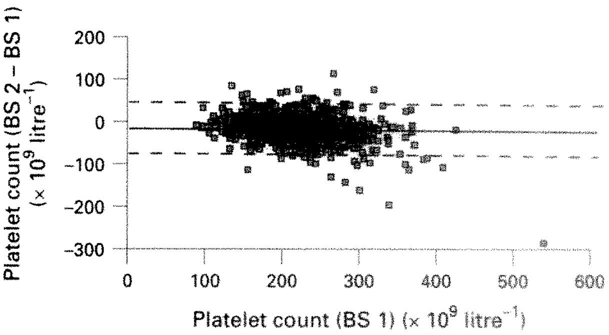

*Figure 1* Variations (in absolute value) in platelet count between the two samples, BS 1 and BS 2, for each woman. These variations (Y axis) in function of the BS 1 value for platelet count (X axis) are shown. Mean variation (—) and 95% confidence limits (- - -) for these variations are also indicated.

### PLATELET COUNT

Mean values for platelet count in BS 1 and BS 2

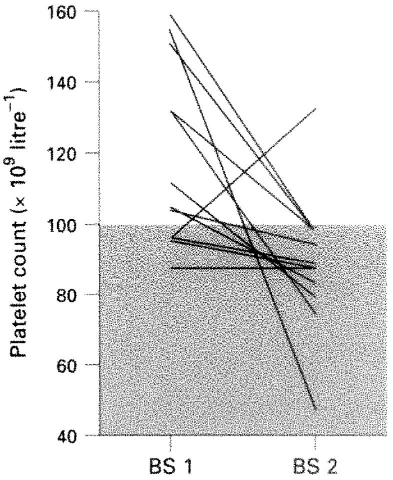

*Figure 2* Variations (in absolute value) in platelet count between the two samples, BS 1 and BS 2, for women who had a platelet count less than $100\times10^9$ litre$^{-1}$ (mean value $-1.96$ SD at BS 2) in either one or both samples. The shaded area indicates the area below $100\times10^9$ litre$^{-1}$.

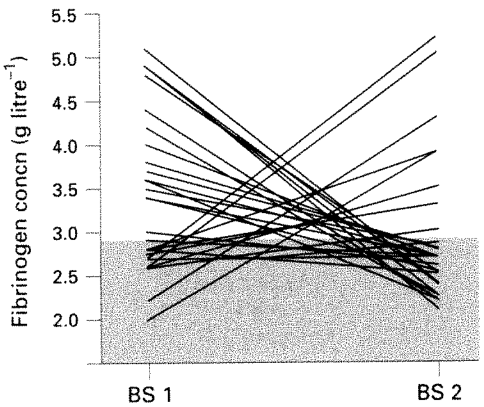

*Figure 3* Variations (in absolute value) in plasma fibrinogen concentration between the two samples, BS 1 and BS 2, for women who had a plasma fibrinogen concentration less than 2.9 g litre$^{-1}$ (mean value $-1.96$ SD at BS 2) in either one or both samples. The shaded area indicates the area below 2.9 g litre$^{-1}$.

were, respectively, 216 (54)$\times10^9$ litre$^{-1}$ (extremes 88–538) and 206 (54)$\times10^9$ litre$^{-1}$ (extremes 48–415). From BS 1 to BS 2, platelet count was variable and unpredictable in all women (fig. 1).

The lower threshold of the 95% confidence limit for platelet count was $100\times10^9$ litre$^{-1}$ (BS 2 mean value $-1.96$ SD$=206-(1.96\times54)=100\times10^9$ litre$^{-1}$). Four women were thrombocytopenic ($<100\times10^9$ litre$^{-1}$) at BS 1. For one patient, platelet count increased to $132\times10^9$ litre$^{-1}$ at BS 2, whereas for the others, platelet count at BS 2 remained less than $100\times10^9$ litre$^{-1}$. Thrombocytopenia ($<100\times10^9$ litre$^{-1}$) appeared in eight other women at BS 2. Therefore, a total of 11 women had platelet counts less than $100\times10^9$ litre$^{-1}$ at BS 2. All of these parturients had platelet counts less than $160\times10^9$ litre$^{-1}$ at BS 1 (fig. 2). Mean variation between the two samples was $-26$ (20) % for these 11 thrombocytopenic patients whereas it was $-3.7$ (14) % in the overall population.

### PT, aPTT AND PLASMA FIBRINOGEN CONCENTRATION

There were no abnormal values for PT or aPTT in either BS 1 or BS 2. Mean values for fibrinogen concentrations in BS 1 and BS 2 were, respectively, 4.6 (0.8) g litre$^{-1}$ (extremes 2.0–7.6) and 4.8 (1.0) g litre$^{-1}$ (extremes 2.1–9.0). The lower threshold of the 95% confidence limit for plasma fibrinogen concentration was 2.9 g litre$^{-1}$ (BS 2 mean value $-1.96\times$SD). Thirteen parturients had fibrinogen concentrations less than 2.9 g litre$^{-1}$ at BS 1. Twenty-six parturients had fibrinogen concentrations less than 2.9 g litre$^{-1}$ at BS 2. For these women, the variation in fibrinogen concentration from BS 1 to BS 2 was $-1.23$ (0.88) g litre$^{-1}$, whereas it was $+0.18$ (0.84) g litre$^{-1}$ in the overall population. As observed with platelet count, BS 1 was not reliable in detecting women with fibrinogen concentrations less than 2.9 g litre$^{-1}$ at BS 2 (fig. 3).

### COAGULATION DISORDERS IN EARLY LABOUR AND PPH

The mode of delivery was vaginal for 677 women and a Caesarean section was performed in the other 120. Among the 677 who had a vaginal delivery, 46 had significant PPH (table 2) and all occurred in patients asymptomatic for haemostasis disorders before delivery. They were all considered as clinically significant haemorrhages requiring volume expansion (Ringer's solution, blood transfusion, or both) and manual uterine exploration. In two patients, hysterectomy was necessary to stop massive haemorrhage. Mean

*Table 2* Number of patients and main clinical characteristics of women who had Caesarean section or vaginal delivery with or without post-partum haemorrhage (PPH). *$P<0.05$ *vs* value in women who had vaginal delivery with no PPH (Student's *t* test)

| | | Vaginal delivery | |
|---|---|---|---|
| | Caesarean sections | PPH | No PPH |
| *n* | 120 | 46 | 631 |
| Age (yr) (mean (range)) | 32.7 (21–45) | 30.9 (21–41) | 31.5 (19–46) |
| Gestational age (weeks) | 39.3 (1.5) | 39.8 (1.2) | 39.5 (1.3) |
| Haematology values in labour ward (BS 2) (mean (SD) | | | |
| Platelet count ($\times10^9$ litre$^{-1}$) | 206 (61) | 185 (59)* | 208 (53) |
| Fibrinogen level (g litre$^{-1}$) | 5.0 (0.9) | 4.3 (1.3)* | 4.9 (1.0) |

*Table 3* Sensitivity specificity, positive and negative predictive values of fibrinogen concentration <2.9 g litre$^{-1}$, at either BS 1 or BS 2, predicting occurrence of PPH

| | Sensitivity (%) | Specificity (%) | Positive predictive value (%) | Negative predictive value (%) |
|---|---|---|---|---|
| Fibrinogen <2.9 g litre$^{-1}$ at | | | | |
| BS 1 | 4.3 | 98.4 | 16.6 | 93.4 |
| BS 2 | 19.6 | 97.8 | 39.1 | 94.3 |

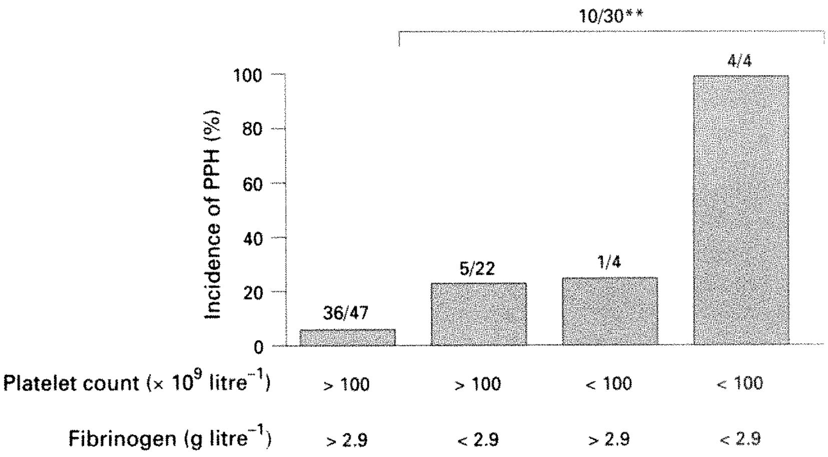

*Figure 4* Incidence of post-partum haemorrhage (PPH) in women with platelet counts or fibrinogen concentrations at BS 2 less than $100 \times 10^9$ litre$^{-1}$ and 2.9 g litre$^{-1}$, respectively. The incidence was significantly different compared with the rate observed in women with both platelet count and fibrinogen concentrations greater than these thresholds (**$P<0.01$; Fischer's exact test). Rates are indicated in percent (Y axis) and absolute values.

decrease in haemoglobin concentration within 24 h post-partum was 4.0 (1.5) g dl$^{-1}$ for these 46 patients.

Platelet count and fibrinogen concentration at BS 2 were significantly lower in women with PPH than in those who did not bleed (table 2). If one or both of these variables were below the corresponding "mean value −1.96 SD" threshold, the incidence of PPH was increased significantly compared with the other women (fig. 4). Sensitivity, specificity, positive and negative predictive values for both BS 1 and BS 2 for low fibrinogen predicting subsequent PPH are presented in table 3.

## Discussion

In our study, the percentage of women with platelet count values less than $100 \times 10^9$ litre$^{-1}$ and less than $150 \times 10^9$ litre$^{-1}$ increased, respectively, from 0.5 to 1.4% and from 7.3 to 12.4% between BS 1 and BS 2. These results are in agreement with those of Rolbin and colleagues who measured platelet count in 1621 healthy women.[9] Only seven (0.4%) and 104 (6.4%) had platelet counts less than 100 and $150 \times 10^9$ litre$^{-1}$, respectively. However, these results were obtained either during pregnancy or in the post-partum period. All patients were asymptomatic, but some had significant thrombocytopenia (lower platelet count $21 \times 10^9$ litre$^{-1}$). Burrows and Kelton found in 1357 healthy women an incidence of 8.3% asymptomatic mild thrombocytopenia (97–$150 \times 10^9$ litre$^{-1}$) during labour.[5]

Gestational thrombocytopenia is quite common but its significance is still unclear. The decrease in platelet count could be related to haemodilution and acceleration of platelet turnover with increased production of platelets from the bone marrow and increased trapping or destruction at the placental level. This quantitative decrease in platelet count could be counterbalanced by a marked increase in platelet reactivity during pregnancy.[13] On the other hand, some authors have described decreased platelet activation during pregnancy[14 15] and suggested the presence of a plasma factor that selectively inhibits prostaglandin-dependent activation.[15] Therefore, it remains difficult in clinical practice to define precisely the clotting capacities of a woman with a mild gestational thrombocytopenia.

The risk of spinal haematoma has been estimated to be approximately 1 in 150 000 after extradural analgesia.[2] Even if the risk of this complication is increased in patients with a low platelet count, it is difficult to define the safe lower threshold for platelet count. The haematological definition of thrombocytopenia is a platelet count less than $150 \times 10^9$ litre$^{-1}$. The lower limit of $100 \times 10^9$ litre$^{-1}$ for platelet count, often judged as "safe" to perform extradural analgesia,[6–8] has no supporting data. In the absence of any other coagulation disorder, some authors would prefer to lower this limit to $80 \times 10^9$ litre$^{-1}$.[16] Nevertheless, some authors do not systematically observe the platelet count before extradural analgesia.[7 8] Rolbin and colleagues estimated that in their institution approximately 5000 thrombocytopenic parturients have benefitted from extradural analgesia over a 30-yr period without any spinal haematomas.[9] The same team has reported the case of uncomplicated extradural analgesia in an asymptomatic parturient whose platelet count was $2 \times 10^9$ litre$^{-1}$ immediately after delivery.[7]

Whatever the significance of these low platelet counts and the acceptable limit, one remaining problem is the choice of the appropriate time to perform a platelet count. Indeed, some authors found a decrease in mean platelet count whereas others reported no change in platelet count during pregnancy.[17] Many anaesthetists consider it sensible to obtain the results of coagulation tests several weeks before extradural analgesia.[1] However, our study showed that the result of this nine month platelet count was useless in predicting platelet count less than $100 \times 10^9$ litre$^{-1}$ during labour.

The nature of the other laboratory tests which are useful before extradural analgesia and their lower "safe value" are still debatable. Coagulation tests such as PT and aPTT measurements have not been studied extensively in obstetric patients but they seem to be less useful for early detection of haemostasis disorders during labour.[18] Indeed, these tests were always normal in our study. Therefore, we believe that these tests should no longer be performed in clinically normal parturients before extradural analgesia.

Fibrinogen concentration increases physiologically during pregnancy.[19 20] A safe lower limit for plasma fibrinogen concentration has not been evaluated, while the safe laboratory lower limit defined for the general population may not be appropriate for pregnant women. Nevertheless, we had to define a lower limit of normality for both of these variables. Therefore, all values for either platelet count or fibrinogen concentration at BS 2 which were below the lower threshold of the corresponding 95% confidence limit were considered as abnormal.

Our study has shown that significant PPH were more frequent when platelet count or fibrinogen concentration, or both, were low in early labour. In previous studies, this association has not been recognized as a significant factor associated with PPH.[12] The significance of the relationship between these mild coagulation abnormalities and the occurrence of PPH is not clear. During pregnancy, biological changes occur such as an increase in many clotting factor concentrations and placental synthesis of plasminogen activator inhibitor. Early in pregnancy, intravascular fibrin deposition can be found in the uteroplacental circulation.[19] This reflects local chronic intravascular coagulation which induces local fibrinolysis.[21 22] These biological changes are associated with mechanical factors that limit the risk of bleeding, such as structural changes in the spiral arteries and myometrial contractions.[6 19] These physiological changes must prepare the pregnant woman for delivery and placental separation and the inherent risk of haemorrhage. In case of failure of the mechanical protective mechanisms, there is an increased need for haemostatic components such as fibrinogen and platelets. We may hypothesize that in such situations there is inadequate compensation which is reflected in a low platelet count and a low fibrinogen plasma concentration. Combs, Murphy and Laros showed that the main clinical variables related to the risk of PPH were prolonged labour and factors associated with uterine atony.[12] If impaired uterine contractility occurred in patients with a low platelet count and fibrinogen concentration, local coagulation factors may not ensure good haemostasis and therefore, at the time of delivery, an increased incidence of PPH could occur. This hypothesis of a relationship between obstetric factors and mild coagulation abnormalities may explain the occurrence of PPH, but this will require further studies.

In clinical practice, detection of coagulation abnormalities, and especially detection of thrombocytopenia, may be important in the management of the obstetric patient. Nevertheless, unhelpful coagulation tests should be avoided. Our results demonstrated that coagulation tests performed several weeks before labour should be abandoned and that PT and aPTT are unnecessary in clinically normal parturients.

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# Effect of progressive haemodilution with hydroxyethyl starch, gelatin and albumin on blood coagulation

G. A. Egli, A. Zollinger, B. Seifert, D. Popovic, T. Pasch and D. R. Spahn

## Summary

We have compared the effects of progressive (30% and 60%) *in vitro* haemodilution with hydroxyethyl starch (HES), gelatin (GEL) and albumin (ALB) with haemodilution using 0.9% saline in 96 patients by thrombelastography. Haemodilution with HES, GEL and ALB significantly ($P<0.05$) compromised coagulation time ($k$), angle $\alpha$ and maximal amplitude (MA), with HES having the most negative effect at 30% and 60% haemodilution ($P<0.05$). Haemodilution with saline significantly affected all variables of blood coagulation and clot lysis measured by thrombelastography, resulting in an increased coagulability at 30% haemodilution. To specifically assess the intrinsic effect of plasma expander molecules on blood coagulation and clot lysis, we analysed the difference between saline diluted blood (same degree of haemodilution) and plasma expander diluted blood. Prolongation of reaction time ($r$) was found for HES at 30% and 60% haemodilution and for ALB at 60% haemodilution and an increase in clot lysis by HES, GEL and ALB became evident. We conclude that HES, GEL and ALB compromised blood coagulation, while the maximum effect was found with HES. (*Br. J. Anaesth.* 1997; **78**: 684–689).

**Key words**
Blood, haemodilution. Measurement techniques, thrombelastography. Blood, coagulation. Blood, replacement.

In recent years there has been increasing awareness of the potential side effects of allogeneic blood products.[1] With increasing use of artificial plasma expanders, their influence on blood coagulation may become clinically relevant.[2] However, assessing the influence of various plasma expanders on blood coagulation is difficult because the observed effect may be a result of an intrinsic effect of the plasma expander molecules in addition to an effect of haemodilution on blood coagulation *per se*. Haemodilution may not necessarily compromise blood coagulation. In contrast, haemodilution with crystalloids may even increase blood coagulation as shown *in vitro*[3] and *in vivo*.[4–6] To standardize the degree of haemodilution and, in particular, to distinguish between the effect of plasma expanders and the effect of haemodilution *per se*, we have assessed *in vitro* the effect of hydroxyethyl starch, gelatin and albumin on blood coagulation compared with saline diluted blood samples using thrombelastography.

## Patients and methods

With approval of the Ethics Committee, a 10-ml blood sample was collected from 126 patients undergoing various surgical procedures. In a pilot study (30 patients) blood was collected during induction of anaesthesia and in the main study (96 patients) blood was collected before induction. Exclusion criteria were known coagulation disorders, prothrombin time less than 85%, non-steroidal anti-inflammatory agents (NSAID) within 24 h before surgery, oral anticoagulation, acetylsalicylic acid (ASA) within 5 days before operation, known liver diseases or increased plasma concentrations of aspartate aminotransferase (AST>50 iu litre$^{-1}$) or alanine aminotransferase (ALT>50 iu litre$^{-1}$), and known renal diseases or increased creatinine concentration (creatinine>120 μmol litre$^{-1}$). Standard thrombosis prophylaxis of low molecular weight heparin administered s.c. (3000 IE, Sandoparin) the evening before surgery was allowed.

Blood coagulation was assessed by thrombelastography (CTEG #3000, Haemoscope, Morton Grove, IL, USA). Whole blood (0.36 ml) is placed in a cuvette which is rotated back and forth. A piston is suspended in the blood, and as coagulation proceeds, fibrin strands form between the walls of the cuvette and the piston. The piston thus becomes increasingly coupled to the motion of the cuvette, and hence the shearing elasticity of the evolving blood clot is detected to yield the TEG trace.[3 6] This TEG trace is described by specific variables. Reaction time ($r$) is the interval between the start of the recording until an amplitude of 2 mm is reached (normal value 12.0 (2.3) mm). It reflects the function of the coagulation factors. Coagulation time ($k$)

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is defined as the time interval from the end of *r* until the amplitude of the TEG tracing reaches 20 mm (normal value 4.2 (1.6) mm); *k* is influenced not only by coagulation factors but also by fibrinogen and the number and function of platelets. Maximum amplitude (MA) of the TEG tracing reflects clot strength as a function of platelets and fibrinogen (normal value 63.5 (4.5) mm). The angle $\alpha$ is formed by the slope of the TEG tracing from the *r* to the *k* value and is, similarly to MA, influenced by the function of platelets and fibrinogen (normal value 60.2 (6.7) °). Clot lysis can be described by the clot lysis index (CLI), defined as the amplitude of the TEG trace at 60 min after MA (A60) divided by MA (CLI=A60/MA×100, %) or by Ly30 and Ly60.[7] The fibrinolysis indexes, Ly30 and Ly60, computed by the current TEG device, are defined as the percentage reduction of the computed area under the curve 30 and 60 min after reaching MA (normal value for Ly30<7.5 % and Ly60<15%). All normal values apply to plastic cups and plastic pins with 1% celite activation (CTEG manual, Haemoscope Corporation, 1990).

The following volume expanders were investigated: hydroxyethyl starch 200 000/0.5 (HES) (Isohes 6%, Laevosan International AG, Zurich, Switzerland), succinylated gelatin (GEL) (Physiogel 4%, Braun Medical, Emmenbrücke, Switzerland) and 5% human serum albumin (ALB) (ZLB Zentrallaboratorium Blutspendedienst SRK, Bern, Switzerland). In pilot studies (30 patients), we found that sodium bicarbonate and $CaCl_2$ had to be added to all volume expanders and also to 0.9% saline such that physiological pH and ionized $Ca^{2+}$ values resulted after *in vitro* haemodilution. However, the amount of sodium bicarbonate and $CaCl_2$ was not the same for different volume expanders. Thus we defined (pre-haemodilution) ranges for pH and ionized $Ca^{2+}$ for all volume expanders and 0.9% saline which resulted in physiological pH and physiological ionized $Ca^{2+}$ after *in vitro* haemodilution. The following ranges were found: HES (pH 6.66–6.92; $Ca^{2+}$ 1.22–1.29 mmol litre$^{-1}$), GEL (pH 7.28–7.40; $Ca^{2+}$ 1.24–1.29 mmol litre$^{-1}$), ALB (pH 7.10–7.24; $Ca^{2+}$ 1.32–1.38 mmol litre$^{-1}$) and saline (pH 6.88–7.45, $Ca^{2+}$ 1.18–1.24 mmol litre$^{-1}$). Adjusting pH and calcium concentration of all volume expanders and 0.9% saline *in vitro* before haemodilution is important because *in vitro* there are no effective homeostatic mechanisms preventing relevant changes in pH and electrolyte concentrations caused by haemodilution with crystalloids or colloids. Without such a correction blood coagulation would have been impaired by low ionized $Ca^{2+}$ and low pH.[8–11]

Blood samples from 96 patients were allocated randomly to one of six groups ($n$=16) to be haemodiluted with HES, GEL or ALB, either by 30% or 60%. In each patient, blood coagulation was assessed simultaneously in native blood, after haemodilution with a volume expander and also after haemodilution to the same degree with saline (see below).

Foaming or frothing was prevented carefully during blood sampling. The first 2 ml were discarded and then 8 ml were sampled in polypropylene syringes. With reverse pipetting the appropriate amount of blood was filled into prewarmed (37.0 °C) polypropylene tubes containing volume expander or saline to prevent cooling of the blood volume expander mixture which might compromise blood coagulation.[11 12] Mixing was performed carefully by filling and half-emptying the pipette five times. The same procedure was performed with native blood so as to prevent activation of the coagulation system through handling. Three minutes after mixing, 1 ml of native blood, 1 ml of volume expander diluted blood and 1 ml of saline diluted blood were filled into tubes containing 1% celite.[13] One minute later (4–5 min after blood withdrawal), 360 µl were pipetted into the thrombelastographic cups. Exactly 6 min after withdrawal of blood, thrombelastography was started.[7] Plastic pins and plastic cups used were put in the TEG at least 10 min before starting the assay. The temperature of the TEG was maintained at 37.0 °C. The remainder of the native and diluted blood was used for blood-gas, electrolyte and haemoglobin measurements (BGElectrolytes and CO-Oximeter, Instrumentation Laboratory, Lexington, MA, USA and Electrolyte 8 Analyser, Nova Biomedica, Waltham, MA, USA).

Unpaired *t* tests were used to compare patient characteristics (Statview 4.02, Abacus Concepts, Inc., Berkeley, CA). Changes caused by *in vitro* haemodilution were analysed by repeated measures analysis of variance (ANOVA) with Greenhouse–Geisser correction (Superanova 1.11, Abacus Concepts, Inc., Berkeley, CA, USA). When this overall ANOVA resulted in a significant haemodilution and plasma expander effect, respectively, *post hoc* paired and unpaired *t* tests with Bonferroni correction were performed. Data are presented as mean (SD) and mean (SEM) as appropriate. $P<0.05$ was considered statistically significant.

## Results

Three were no differences in the HES, GEL and ALB groups in patient characteristics (table 1) or baseline data (table 2, figs 1, 3).

Haemodilution with HES, GEL, ALB and saline resulted in a similar decrease in haemoglobin concentration (table 2). Ionized $Ca^{2+}$ concentration was stable during haemodilution in the HES and GEL groups but decreased minimally in the ALB group at

*Table 1* Characteristics of patients in the HES, GEL and ALB groups. Data are mean (SD or range). There are no significant differences between groups. LMWH=low molecular weight heparin

| | HES ($n$=32) | GEL ($n$=32) | ALB ($n$=32) |
|---|---|---|---|
| Age (yr) | 53.1<br>(18–74) | 51.6<br>(19–80) | 52.3<br>(21–79) |
| BMI (kg m$^{-2}$) | 25.8 (3.6) | 25 4 (3.2) | 25.5 (3.7) |
| Sex (F/M) | 11/21 | 7/25 | 9/23 |
| Creatinine (µmol litre$^{-1}$) | 90 (11) | 93 (10) | 89 (20) |
| Platelet count (10$^3$ µl$^{-1}$) | 235 (61) | 224 (46) | 225 (58) |
| LMWH administered | 18 of 32 | 18 of 32 | 19 of 32 |
| Incidence of carcinoma | 3 of 32 | 5 of 32 | 6 of 32 |

*Table 2* Ionized $Ca^{2+}$ concentration ($Ca^{2+}$), pH (pH) and haemoglobin concentration (Hb) after haemodilution (HD) with HES, GEL, ALB and saline. Data are mean (SD). Significantly different *($P<0.05$) from native blood

| | HES ($n=16$) | GEL ($n=16$) | ALB ($n=16$) | Saline ($n=48$) |
|---|---|---|---|---|
| Hb (g $dl^{-1}$) | | | | |
| 0% HD | 14.07 (1.55) | 14.35 (1.39) | 14.55 (1.20) | 14.32 (1.39) |
| 30% HD | 9.84 (1.19)* | 10.21 (1.00)* | 10.31 (0.82)* | 10.16 (1.01)* |
| 60% HD | 5.76 (0.63)* | 5.67 (0.55)* | 5.88 (0.54)* | 5.85 (0.58)* |
| $Ca^{2+}$ (mmol $litre^{-1}$) | | | | |
| 0% HD | 1.23 (0.04) | 1.24 (0.04) | 1.23 (0.04) | 1.23 (0.04) |
| 30% HD | 1.23 (0.03) | 1.25 (0.04) | 1.19 (0.03)* | 1.22 (0.03)* |
| 60% HD | 1.24 (0.02) | 1.25 (0.03) | 1.19 (0.04)* | 1.21 (0.03)* |
| pH | | | | |
| 0% HD | 7.43 (0.03) | 7.43 (0.02) | 7.42 (0.03) | 7.43 (0.03) |
| 30% HD | 7.42 (0.02)* | 7.41 (0.02)* | 7.42 (0.03) | 7.41 (0.02)* |
| 60% HD | 7.40 (0.03)* | 7.42 (0.02)* | 7.41 (0.05) | 7.41 (0.03)* |

30% and 60% haemodilution (table 2). pH was stable during haemodilution with ALB and decreased minimally during haemodilution with HES and GEL (table 2). Also, during haemodilution with saline, the ionized $Ca^{2+}$ concentration and pH decreased minimally at 30% and 60% haemodilution (table 2). However, ionized $Ca^{2+}$ concentration and pH were within the physiological range after haemodilution with all volume expanders and saline (table 2).

Compared with native blood, progressive haemodilution with HES, GEL and ALB did not affect reaction time (*r*) (fig. 1A) but compromised the rapidity of clot formation, as manifested by an increase in coagulation time (*k*) and a decrease in the clot formation rate (angle α) (fig. 1B, C). With HES, this was significant at 30% haemodilution; with GEL and ALB, significant changes were observed only at 60% haemodilution. The strength of the clot (MA) was decreased by HES, GEL and ALB at 30% and 60% haemodilution (fig. 1D). Thus HES had the most negative effect on *k*, angle α and MA. Clot lysis at 30 or 60 min was not affected by haemodilution (fig. 1E, F). No individual patient had pathological clot lysis caused by haemodilution, that is Ly30>7.5 % or Ly60>15%.

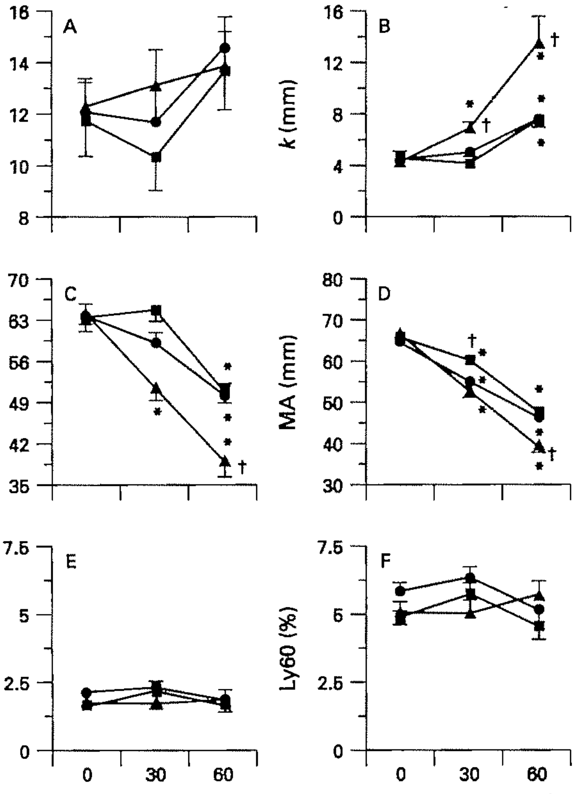

*Figure 1* Effect of progressive (30%, 60%) *in vitro* haemodilution with hydroxyethyl starch (▲), gelatin (●) and albumin(■) on blood coagulation, as assessed by thrombelastography: reaction time (*r*) (A), coagulation time (*k*) (B), angle α (Ang α) (C), maximal amplitude (MA) (D), lysis after 30 min (Ly30) (E) and lysis after 60 min (Ly60) (F). Data are mean (SEM). Significantly different (*$P<0.05$) from native blood; significantly different (†$P<0.05$) from other groups.

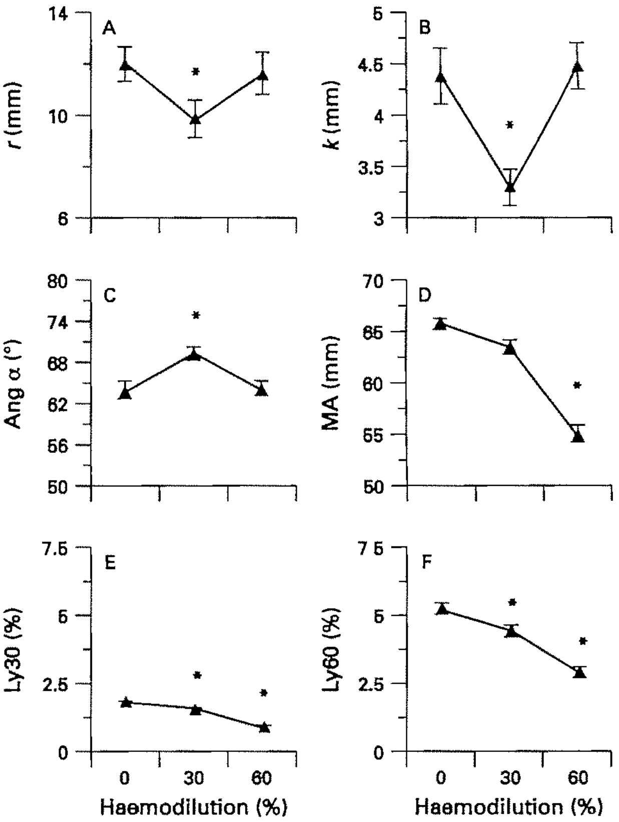

*Figure 2* Effect of progressive (30%, 60%) *in vitro* haemodilution with saline (▲) on blood coagulation as assessed by thrombelastography: reaction time (*r*) (A), coagulation time (*k*) (B), angle α (Ang α) (C), maximal amplitude (MA) (D), lysis after 30 min (Ly30) (E) and lysis after 60 min (Ly60) (F). Data are mean (SEM). Significantly different (*$P<0.05$) from native blood.

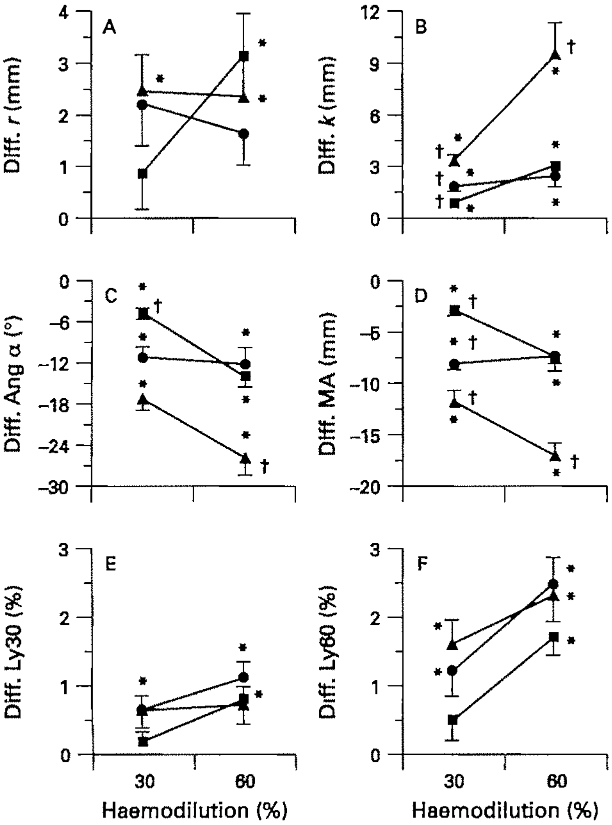

*Figure 3* Effect of progressive (30%, 60%) *in vitro* haemodilution with hydroxyethyl starch (▲), gelatin (●) and albumin(■) on blood coagulation as assessed by thrombelastography in comparison with haemodilution with 0.9% saline, expressed as absolute difference (Diff.) of values (expander minus saline): reaction time (Diff. *r*) (A), coagulation time (Diff. *k*) (B), angle α (Diff. Ang α) (C), maximal amplitude (Diff. MA) (D), lysis after 30 min (Diff. Ly30) (E) and lysis after 60 min (Diff. Ly60) (F). Data are mean (SEM). Significantly different (*$P<0.05$) from 0; significantly different (†$P<0.05$) from other groups.

To specifically assess the intrinsic effect of plasma expander molecules on blood coagulation, we first analysed the effect of haemodilution with saline *per se* (compared with native blood). At 30% haemodilution, reaction time (*r*) and coagulation time (*k*) decreased and clot formation rate (angle α) increased. At 60% haemodilution, all three variables recovered (fig. 2A–C). MA was compromised at 60% haemodilution, and clot lysis at 30 and 60 min (Ly30 and Ly60) showed progressive decrease with increasing haemodilution (fig. 2D–F).

The intrinsic effect of plasma expander molecules on blood coagulation may thus be assessed by analysing the difference between saline diluted blood (same degree of haemodilution) and plasma expander diluted blood. Haemodilution with HES resulted in a longer reaction time (*r*) at 30% and 60% haemodilution compared with saline haemodilution, and ALB resulted in a longer reaction time (*r*) at 60% haemodilution (fig. 3A). Coagulation time (*k*) was prolonged by haemodilution with HES, GEL and ALB at 30% and 60% haemodilution compared with saline haemodilution (fig. 3B), and also clot formation rate (angle α) was less during 30% and 60% haemodilution using HES, GEL and ALB than during haemodilution with saline (fig. 3C). Furthermore, the decrease in the strength of the clot, that is the decrease in MA, was more pronounced during 30% and 60% haemodilution with HES, GEL and ALB compared with haemodilution using saline (fig. 3D). HES had the most negative effect on *k*, angle α and MA. Haemodilution with GEL and ALB resulted in increased clot lysis at 30 min (Ly30) in comparison with haemodilution with saline (fig. 3E), and clot lysis at 60 min (Ly60) was increased more during haemodilution with HES, GEL and ALB compared with haemodilution with saline (fig. 3F).

There were no differences between patients with and without cancer, either at baseline or at any degree of haemodilution with any volume expander tested (data not shown).

## Discussion

We have demonstrated that blood coagulation was compromised by *in vitro* haemodilution using hydroxyethyl starch, gelatin or albumin. However, hydroxyethyl starch had the most pronounced effect. Also, when the effect of haemodilution with saline is considered, hydroxyethyl starch, gelatin and albumin also increased clot lysis.

Because of increasing awareness of the potential side effects of allogeneic blood products, volume expanders are used increasingly to treat surgical blood loss.[1] Thus the side effects of volume expanders such as interference with blood coagulation may become clinically relevant. In this study we found that while hydroxyethyl starch had the most pronounced effect, *all* volume expanders showed qualitatively similar effects, namely a marked decrease in the strength of the clot (MA) and rapidity of clot formation (angle α), and also an increase in coagulation time (*k*) (figs 1, 3). This pattern is compatible with platelet dysfunction[14] and with previous reports of a decrease in all factor VIII moieties produced by hydroxyethyl starch and dextran infusions,[15–20] which might result in platelet dysfunction.[21] However, the decrease in factor VIII was not observed when dextran or hydroxyethyl starch was added *in vitro*.[17 22] These *in vitro* studies, however, were performed in citrated plasma to prevent clotting and thus may not be representative of the present study because blood coagulation in this study was not inhibited but progressed during thrombelastography measurement. When blood coagulation is not inhibited, hydroxyethyl starch and dextran solutions can precipitate coagulation factors also *in vitro*[23] and thus compromised blood coagulation during haemodilution might be caused by reduced clotting factor activity, in particular factor VIII.

We found significant impairment of blood coagulation with hydroxyethyl starch but also with albumin and gelatin (figs 1, 3). Thus during profound haemodilution, blood coagulation may be compromised irrespective of the volume expander used. Indeed, recent data suggest that abnormal haemostasis may develop before compromise of global tissue oxygen delivery and consumption.[2]

The effects of plasma expanders on clot lysis have not been investigated fully. In the presence of hydroxyethyl starch, faster transformation of fibrinogen to fibrin has been shown.[24 25] This fibrin was shown to be less stable as evidenced by a shortened urokinase-activated clot lysis time suggesting enhanced fibrinolysis.[24 25] Also, gelatin has been shown to be incorporated into developing blood clots and thus potentially interfere with fibrin polymerization.[26] Similarly, we also found progressively augmented clot lysis for all three plasma expanders compared with saline. This effect, however, was apparent only when the influence of haemodilution with saline *per se* on clot lysis was taken into account (fig. 3). Despite this augmentation, clot lysis was, on average, still within normal ranges and thus may be of limited clinical relevance.

Interestingly, moderate haemodilution with crystalloids appeared to augment blood coagulation (fig. 2) which is in keeping with earlier *in vitro*[3] and *in vivo* observations.[4–6] Recently, Ruttmann, James and Viljoen[3] described a hypercoagulable state at 20% haemodilution with saline, as evidenced by a shortened reaction time (*r*) and an increased rapidity of clot formation (*k* and angle $\alpha$). At 30% haemodilution with saline, we also found a shortened reaction time (*r*) and increased rapidity of clot formation (*k* and angle $\alpha$) (fig. 2). At 30% haemodilution with gelatin, however, we did not observe such an augmentation of blood coagulation (fig. 1) compared with Ruttmann, James and Viljoen,[3] who also described a shortened reaction time (*r*) and increased rapidity of clot formation (*k* and angle $\alpha$) at 20% haemodilution with gelatin. The difference might be explained by the more profound degree of haemodilution produced in this study. Interestingly, although we did not observe a hypercoagulable state at 30% haemodilution with gelatin, *k* and angle $\alpha$ were unchanged and became compromised only at 60% haemodilution, indicating that the degree of haemodilution may be crucial for changes in blood coagulation during haemodilution.

The mechanisms by which blood coagulation is facilitated during moderate haemodilution with saline are largely unknown. One might hypothesize, however, that the anticoagulant activity of blood may be compromised more than the procoagulant activity during moderate haemodilution, resulting in a hypercoagulable state. With advanced haemodilution also, procoagulant activity may become diluted and the net result at profound haemodilution is compromised blood coagulation, as observed in this study at 60% haemodilution (fig. 2). Interestingly, we also found reduced clot lysis during haemodilution with saline (fig. 2). This effect was most prominent at profound haemodilution, that is at 60% haemodilution with saline. Further studies are necessary to elucidate these findings.

It is difficult to extrapolate our findings to clinical practice. Intraoperative use of volume expanders such as albumin and gelatin may compromise blood coagulation to a lesser extent than hydroxyethyl starch. However, in the postoperative period, a period characterized by a hypercoagulable state, hydroxyethyl starch may be beneficial in reducing the risk of thrombosis.[27]

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# Pharmacokinetics and pharmacokinetic–dynamic modelling of rocuronium in infants and children

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## Summary

We have determined the pharmacokinetics and pharmacokinetic–pharmacodynamic relationship of rocuronium in infants and children. We studied infants ($n$=5, 0.1–0.8 yr) and children ($n$=5, 2.3–8 yr), ASA II, in the ICU while undergoing artificial ventilation under i.v. anaesthesia with an arterial cannula *in situ* and the EMG of the adductor pollicis muscle was monitored. Rocuronium 0.06 (infants) and 0.09 (children) mg $kg^{-1}$ $min^{-1}$ was given i.v. over ±5 min until 85% neuromuscular block was obtained. Arterial blood samples were obtained over 240 min. Plasma concentrations were measured by HPLC. Pharmacokinetic–dynamic variables were calculated using the Sheiner model and the Hill equation. Statistical analysis was performed using the Mann–Whitney $U$ test ($P<0.05$). The mean administered dose was 0.32 (SD 0.08) mg $kg^{-1}$ and 0.4 (0.1) mg $kg^{-1}$ for infants and children, respectively. Infants differed from children in plasma clearance (4.2 (0.4) *vs* 6.7 (1.1) ml $min^{-1}$ $kg^{-1}$), distribution volume at steady state (231 (32) *vs* 165 (44) ml $kg^{-1}$), mean residence time (56 (10) *vs* 26 (9) min), concentration in the effect compartment at 50% block (1.2 (0.4) *vs* 1.7 (0.4) mg $litre^{-1}$) and the slope of the concentration–effect relationship (5.7 (1.3) *vs* 3.9 (0.5)). Calculated mean $ED_{90}$ values were 0.26 and 0.34 mg $kg^{-1}$ for infants and children, respectively. The time course of neuromuscular block after equipotent doses did not differ. (*Br. J. Anaesth.* 1997; **78**: 690–695).

**Key words**
Neuromuscular block, rocuronium. Infants. Children. Pharmacokinetics, rocuronium. Pharmacodynamics.

Rocuronium is an intermediate-acting non-depolarizing neuromuscular blocking agent that has a faster onset of action than other non-depolarizing neuromuscular blocking agents.[1] There are only two studies comparing the neuromuscular effects of rocuronium in infants with those in children.[2 3] These investigators obtained different results in that Woelfel and colleagues found that a fixed dose of rocuronium 0.6 mg $kg^{-1}$ had a longer neuromuscular blocking effect and a slower recovery in infants than in children.[2 4] Taivainen and colleagues administered individually determined $ED_{95}$ doses of rocuronium to infants, children and adults and found a similar duration of effect and recovery rate of neuromuscular function in all three age groups.[3] These apparently conflicting results may be explained by the pharmacokinetics of rocuronium. However, pharmacokinetic data currently available for rocuronium in infants are limited and cannot be used to explain the above pharmacodynamic differences.[5] We designed a study to analyse the pharmacokinetics and pharmacodynamic–kinetic relationship of rocuronium in infants and children in order to rationalize these apparently conflicting results in the literature and to contribute to the development of rational dose regimens.

## Patients and methods

After obtaining institutional Ethics Committee approval and parental written informed consent, we studied five infants and five children, ASA II, in the intensive care unit during stable recovery from elective tracheal or cardiovascular surgery, that is in a state of haemodynamic stability without supportive medication, normal peripheral (>32.5 °C) and core (>36.5 °C) temperatures, and normal values for blood chemistry, plasma proteins and packed cell volume. All patients were studied in the same intensive care unit. This site was chosen to guarantee stable cardiovascular and respiratory status of the patients, in the absence of surgical manipulations or bleeding during the study period, to allow an arterial cannula for arterial sampling to obtain reliable plasma concentrations for modelling. Surgical procedures in the patients are listed in table 1. Patients receiving medications or with diseases known to affect neuromuscular function, or patients with signs of hepatic or renal dysfunction were excluded.

Patients were routinely sedated and their lungs ventilated with the aid of i.v. bolus doses of

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morphine and midazolam. Before calibration of the neuromuscular device patients received thiopentone 2–6 mg $kg^{-1}$ and alfentanil 20–80 μg $kg^{-1}$ to guarantee a sufficient level of anaesthesia during the period of neuromuscular block. Standard monitoring included ECG, pulse oximetry, continuous core and palmar skin temperature monitoring, and invasive arterial pressure measurement.

### NEUROMUSCULAR MONITORING AND SEQUENCE OF EVENTS

The arm opposite to the arm with the arterial cannula was used for neuromuscular measurements, that is adductor pollicis muscle electromyography (Relaxograph, Datex, Finland) after supramaximal train-of-four (TOF) stimulation (4 stimuli at a frequency of 2 Hz every 10 s). Surface stimulating electrodes were attached over the ulnar nerve on the wrist and recording electrodes over the adductor pollicis muscle, over the proximal volar surface of the index finger and at the radial side of the wrist distal to the stimulating electrodes.[6] Palmar skin temperature was obtained from the same hand. A stable calibration signal of the electromyographic trace was awaited before rocuronium was administered. Neuromuscular block was defined as percentage depression of the first EMG twitch response (T1) of the TOF compared with the baseline calibration response. After infusion of rocuronium, neuromuscular function was recorded in every patient until full spontaneous recovery of the EMG response had occurred. The stable twitch response after recovery (Tc) was used as a reference value to calculate EMG recovery data. The time of maximal neuromuscular block after rocuronium infusion and times from maximum block until recovery of T1 to 25% and 75% of Tc and to a train-of-four ratio (T4/T1) of 0.7 ($DUR_{0.7}$) were calculated. The recovery index ($RI_{25-75\%}$, time of T1 recovery from 25% to 75% of Tc) was derived from these data.

Rocuronium was administered by a continuous infusion joined by a needle to a rubber attachment of a steadily running central venous cannula. In five infants rocuronium, diluted in physiological saline to a concentration of 0.1 mg $ml^{-1}$, was infused end to side to a running peripheral venous cannula at a rate of 0.06 mg $kg^{-1}$ $min^{-1}$ until a decrease in twitch height of 85% was obtained. The infusion was then stopped to prevent occurrence of complete block. In five children, rocuronium, diluted in physiological saline to a concentration of 0.3 mg $ml^{-1}$, was infused via a peripheral venous cannula at a rate of 0.09 mg $kg^{-1}$ $min^{-1}$ also until 85% block was obtained.

Blood samples (0.5 ml) were obtained from an arterial cannula at the following times: one blank sample immediately before administration of rocuronium; five samples during onset of neuromuscular block at various degrees of block, that is at 1 and 2 min after the start of infusion and at approximately 20, 50, and 80% of block; one sample at maximum block; three samples at approximately 20%, 55% and 90% recovery of T1; and at 30, 45, 60, 90, 120, 180 and 240 min after disconnection of the infusion. Total sampling volume was restricted to less than 2% of the circulating blood volume of infants and to less than 1% of the circulating blood volume of children. Samples were stored in lithium heparinized tubes at room temperature until centrifugation, which took place within 4.5 h after the start of sampling. Plasma samples were stored at −20 °C after centrifugation. After completion of the study all samples were transported on dry ice to the analytical laboratory and stored at −18 °C until analysis.

### SAMPLE ANALYSIS

Concentrations of rocuronium (Org 9426) and its putative derivatives, 17-desacetyl-rocuronium (Org 9943) and 16-N-desallyl-rocuronium (Org 20860), were analysed by HPLC as described previously.[7] Using this method precision was almost independent of concentration and was 8%, 7% and 12% for rocuronium (10–20 000 ng $ml^{-1}$), Org 9943 (20–20 000 ng $ml^{-1}$) and Org 20860 (20–20 000 ng $ml^{-1}$), respectively. The accuracy for rocuronium, expressed as percentage recovered of the added amount, was 86%, 103%, 107% and 98% at concentrations of 10, 1000, 5000 and 10 000 ng $ml^{-1}$, respectively. At 20 and 200 ng $ml^{-1}$, accuracy was 92% and 106% for Org 9943, and 93% and 111% for Org 20860, respectively. The lower limit of quantification, defined as the lowest concentration that could be determined with a precision and accuracy greater than 15%, was 10, 20 and 20 ng $ml^{-1}$ for rocuronium, Org 9943 and Org 20860, respectively.

### PHARMACOKINETIC ANALYSIS

Pharmacokinetic analysis was based on iterative, non-linear, least-squares regression analysis by the computer program Multifit using the Marquardt minimizing algorithm.[8] Initial estimates were obtained by a stripping procedure. For each individual patient the parameters of a two- or three-exponential equation were fitted to the logarithm of the plasma concentration–time data pairs, assuming a constant relative error. The choice between a two- or three-compartment model was made on the $F$ test, accepting a more complex model as significantly better fitting if $P<0.05$. Relevant pharmacokinetic variables were calculated using standard equations, assuming the elimination to take place from the central compartment.[9]

### PHARMACOKINETIC–DYNAMIC MODELLING

The concentration–effect data were analysed using the computer program PkPdFit, the T1 data of the EMG and the values of the coefficients and exponents of a multiexponential equation, describing the concentration *vs* time data in plasma. For each individual patient the variables of the model of Sheiner and colleagues,[10] that is the rate constant between plasma and effect compartment ($k_{eo}$), the concentration in the effect compartment at 50% block ($EC_{50}$) and the sigmoidicity coefficient of the Hill equation ($\gamma$) were fitted to the effect using equal weight for each measurement. The fit was optimized with Simplex as the minimizing algorithm,[11] using sets of initial estimates obtained from previous fits. From these data individual $ED_{90}$ values, that is individual bolus doses resulting in 90% block, were derived.

### STATISTICAL ANALYSIS

All data are presented as mean (SD), [range] and {median} unless otherwise stated. Comparisons between data obtained in infants and children were made using the Mann–Whitney $U$ test. Pharmacokinetic–dynamic variables were related to age and weight by linear regression. $P<0.05$ was considered as an indicator of statistically significant difference.

The computer programs Multifit and PkPdFit were written by one of the authors (J. H. P.).

## Results

### PHARMACODYNAMICS

Patient data are shown in table 1. Tracheal resections had been performed 7 and 11 days before the study while other procedures had been finished 3–20 h before the start of the modelling study. All open heart surgical procedures were performed under normothermic conditions with a mean duration of extracorporeal perfusion of 33 (13) min. Mean time between the end of extracorporeal perfusion and initiation of this study was 7.9 h. The interval between the last dose of intraoperative neuromuscular blocking agent and the start of the modelling study was always more than 10 times the elimination half-life of the blocker given during operation. None of the patients had infusions of vasoactive drugs. Core and palmar skin temperatures did not differ between the groups during the study and averaged 36.9 (0.3) °C and 34.6 (1.5) °C, respectively. Mean duration of calibration was 16 (8) min. In infants, 0.32 (0.08) mg $kg^{-1}$ of rocuronium established 96.9 (2.9) % block in 6.6 (1.6) min. In children, these values were 0.4 (0.1) mg $kg^{-1}$, 96.5 (0.7)% and 5.9 (1.4) min, respectively (ns). $RI_{25-75\%}$ and $DUR_{0.7}$ were 9.1 (4.7) and 21.5 (11.8) min in infants, and 6.3 (0.7) and 14.0 (1.1) min in children, respectively (ns).

### PHARMACOKINETICS

The duration of rocuronium infusion was 5.3 (1.4) and 4.5 (1.1) min in infants and children, respectively. The dose administered was 1.21 (0.06) and 1.2 (0.05) times the individual $ED_{90}$ dose (calculated using individual PK/PD data) for infants and children, respectively. For all patients a three-compartment model fitted the plasma concentration *vs* time data significantly better than a two-compartment model. The residual coefficient of variation of the three-compartmental fits showed ranges and median values of [4.2–7.7%] {5.9%} and [7.7–20.9%] {13.1%} for infants and children, respectively. A representative example is presented in figure 1.

*Table 1* Patient data and surgical procedures. (number or mean (SD) [range])

| | Infants | Children |
|---|---|---|
| Surgical procedure (*n*) | | |
| Tracheal resection | 2 | — |
| Aortic valvulotomy | 1 | — |
| Aortic coarctation resection | 2 | — |
| Atrial septum closure | — | 4 |
| Ventricular septum closure | — | 1 |
| Age (yr) | 0.5 [0.1–0.8] | 5.4 [2.3–8.0] |
| Body weight (kg) | 6.0 (2.1)<br>[4.7–9.6] | 19.1 (4.9)<br>[13.8–27] |

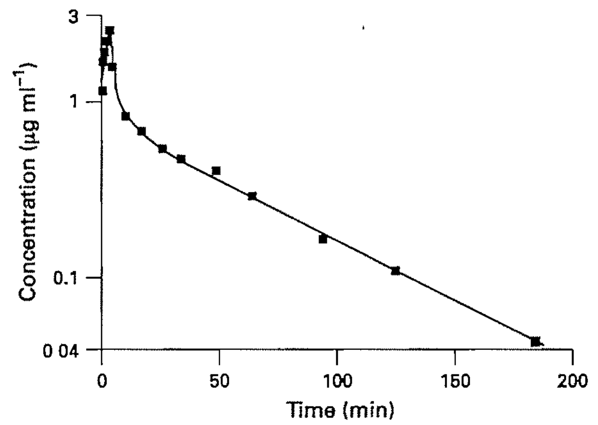

*Figure 1* Representative example of a three-compartmental fit of plasma concentration decay of rocuronium in an infant.

*Table 2* Pharmacokinetic and pharmacokinetic–dynamic variables of rocuronium, administered as an infusion in infants ($n=5$) and children ($n=5$). The rate and the duration of infusion were adapted to obtain maximum block of approximately 95% within 5 minutes of the start of the infusion. Data are mean (SD) [range]). $Cl_{pl}$ is the plasma clearance; $Cl_{12}$ and $Cl_{13}$=distribution clearance to the second and third compartment, respectively; $V_1$, $V_2$ and $V_3$=volumes of the central, second and third compartments, respectively; $V^{ss}$=volume of distribution at steady state; $MRT_{iv}$=mean residence time after an i.v. bolus dose; $k_{e0}$=rate constant of equilibration between central and effect compartments; $EC_{50}$=concentration in the effect compartment at 50% neuromuscular block; γ (gamma)=slope of the concentration–effect relationship in the effect compartment; $ED_{90}$=calculated bolus dose resulting in 90% block

| Variable | Infants | Children | *P* |
|---|---|---|---|
| $Cl_{pl}$ (ml min$^{-1}$ kg$^{-1}$) | 4.19 (0.43)<br>[3.88–4.93] | 6.66 (1.05)<br>[5.65–8.09] | <0.01 |
| $Cl_{12}$ (ml min$^{-1}$ kg$^{-1}$) | 15.1 (4.0)<br>[8.8–19.2] | 10.4 (2.2)<br>[7.5–13.2] | ns |
| $Cl_{13}$ (ml min$^{-1}$ kg$^{-1}$) | 3.24 (3.55)<br>[1.31–9.57] | 1.69 (0.63)<br>[0.64–2.16] | ns |
| $V_1$ (ml kg$^{-1}$) | 35.4 (5.4)<br>[28.0–43.6] | 34.7 (12.8)<br>[16.1–44.8] | ns |
| $V_2$ (ml kg$^{-1}$) | 87 (37)<br>[49–142] | 44 (16)<br>[26–62] | <0.05 |
| $V_3$ (ml kg$^{-1}$) | 108 (16)<br>[89–133] | 86 (34)<br>[49–139] | ns |
| $V^{ss}$ (ml kg$^{-1}$) | 231 (32)<br>[202–283] | 165 (44)<br>[120–214] | <0.05 |
| $MRT_{iv}$ (min) | 55.6 (9.9)<br>[41–66.9] | 25.6 (8.9)<br>[14.8–37.9] | <0.01 |
| $k_{e0}$ (min$^{-1}$) | 0.25 (0.08)<br>[0.17–0.34] | 0.32 (0.06)<br>[0.24–0.37] | ns |
| $EC_{50}$ (mg litre$^{-1}$) | 1.19 (0.38)<br>[0.79–1.62] | 1.65 (0.38)<br>[1.20–2.02] | <0.05 |
| γ | 5.74 (1.28)<br>[4.78–7.97] | 3.91 (0.51)<br>[3.12–4.56] | <0.01 |
| $ED_{90}$ (mg.kg$^{-1}$) | 0.261 (0.066)<br>[0.190–0.300] | 0.335 (0.077)<br>[0.255–0.451] | ns |

In infants, there was a significantly larger volume of distribution at steady state ($V^{ss}$), lower plasma clearance ($Cl_{pl}$), and consequently a longer mean residence time ($MRT_{iv}$) (table 2). The volume of the central compartment was similar in both age groups (table 2). There was a significant positive relationship for age (yr) and $Cl_{pl}$ (ml $min^{-1}$ $kg^{-1}$) ($Cl_{pl}$=0.403 age+4.25; $P$=0.005), whereas there were significant inverse relationships for age and $V^{ss}$ (ml $kg^{-1}$) ($V^{ss}$=−14.1 age+239; $P$=0.0019), and age and $MRT_{iv}$ (min) ($MRT_{iv}$=−5.20 age+55.8; $P$=0.0012). Similar relationships existed for body weight (kg) and $Cl_{pl}$ ($Cl_{pl}$=0.142 BW+3.65; $P$=0.019), body weight and $V^{ss}$ ($V^{ss}$=−5.30 BW+264; $P$=0.0041) and body weight and $MRT_{iv}$ ($MRT_{iv}$=−2.00 BW+65.7; $P$=0.0018). Potential metabolites of rocuronium in plasma were not detected.

### PHARMACOKINETIC–PHARMACODYNAMIC MODELLING

The goodness of the PK/PD fits ($r^2$) showed ranges and median values of [0.9912–0.9980] {0.9971} and [0.9925–0.9951] {0.9942} for infants and children, respectively. The ranges and median values of the residual SD, expressed as percentage twitch height depression, were [1.5–3.4] {1.9} and [2.2–2.9] {2.4} for infants and children, respectively. A representative example is presented in figure 2.

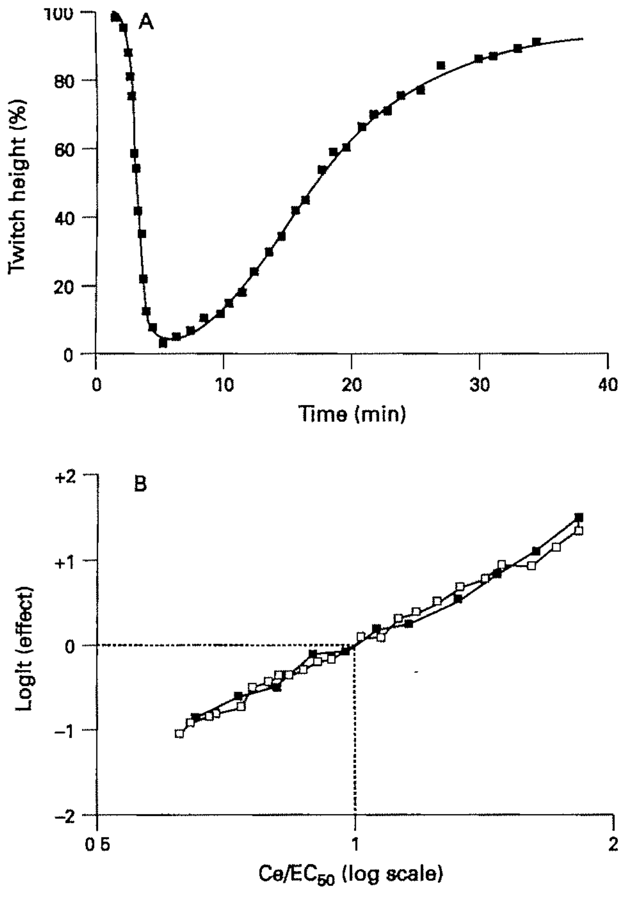

*Figure 2* Example of a pharmacodynamic–pharmacokinetic fit in an infant. A: Effects actually measured (■) with the curve fitted to them. B: Concentration–effect (logit scale) relationship in the effect compartment (■, onset □, offset).

The results of the modelling are presented in table 2. There was a significant inverse correlation for age and $\gamma$ ($\gamma$=−0.30 age+5.71; $P$=0.030), and for BW and $\gamma$ ($\gamma$=−0.13 BW−6.45; $P$=0.013).

## Discussion

This study was carried out under conditions that may differ from those in the operating theatre and in postoperative cardiac surgery patients. Although this may create limitations, we believe that the data may well be valid for developing dose regimens for general anaesthetic practice for the following reasons. (1) Our time course results were in agreement with those of other investigators, obtained in comparable age groups. (2) Our simulations with the PK/PD data predicted findings obtained previously for infants and children (see below). (3) Our patients were in a stable cardiovascular state without supportive medication and had normal values for blood chemistry, plasma proteins and packed cell volume. (4) The study was not commenced before at least 10 half-lives of the neuromuscular blocking agent used during operation had elapsed.

### PHARMACODYNAMICS

We found a similar time course of neuromuscular recovery after an $ED_{95}$ dose of rocuronium administered by infusion in infants and children. This result supports the study of Taivainen and colleagues.[3] Why, then, did Woelfel and colleagues find that after a constant dose of rocuronium 0.6 mg $kg^{-1}$, infants showed recovery times twice as long as those of children?[2 4] Our pharmacokinetic–pharmacodynamic data allowed us to model a pharmacokinetic–dynamic relationship in each individual patient for any dose of rocuronium. We simulated the time course of action of an individual $ED_{90}$ and of a fixed dose of 0.6 mg $kg^{-1}$ in infants and children (fig. 3).

Figure 3 demonstrates clearly how infants show a duration of effect of rocuronium twice as long as that of children after a constant dose of 0.6 mg $kg^{-1}$, despite similar time courses after an individual $ED_{90}$. If a dose of 0.6 mg $kg^{-1}$ is replaced by an intubating dose of twice the mean $ED_{90}$ values in infants and children, the difference becomes less pronounced but is still clinically relevant. $Dur_{25\%}$ of intubating doses (2×$ED_{90}$, i.e. 0.52 mg $kg^{-1}$ for infants and 0.67 mg

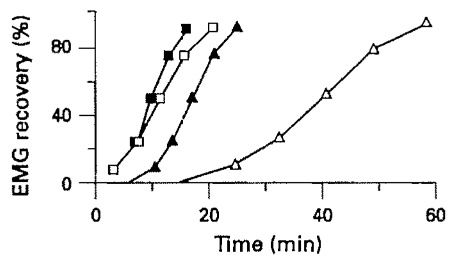

*Figure 3* Simulated time course of action in infants (open symbols) and children (closed symbols) of an $ED_{90}$ dose (□, ■) and of a dose of 0.6 mg $kg^{-1}$ (△, ▲) of rocuronium using the model according to Sheiner and colleagues[10] and the fitted values for the variables obtained in this study.

$kg^{-1}$ for children), calculated on the basis of the model, were 24 (8) and 14 (2) min and $RI_{25-75\%}$ 16 (7) and 8 (1) min for infants and children, respectively. Although our models in infants and children were based on data obtained in a limited number of patients under stable conditions in the postoperative period, their validity for prediction of the time course in these categories appears good because the outcome is supported in studies in which pharmacodynamic characteristics of different doses of rocuronium in paediatric patients have been evaluated.[2–4]

### PHARMACOKINETICS

We found several important pharmacokinetic differences between infants and children. $Cl_{pl}$ of rocuronium was significantly smaller while $V^{ss}$ was greater in infants than in children. This resulted in an $MRT_{iv}$ which was twice as long in infants as in children. These kinetic differences between infants and children resulted in protracted recovery of neuromuscular function in infants after a large bolus dose or repeated doses, as demonstrated by the modelling results shown in figure 3.

O'Kelly and co-workers also found positive correlations of weight-normalized clearance with age and weight.[5] For children aged 1–8 yr with a body weight of 10–25 kg, their results were in good agreement with our findings, as illustrated in figure 4.

Deviation of the results of our study in infants from those of O'Kelly and co-workers could reflect the method of data analysis used by O'Kelly and colleagues, who pooled data of children of various ages in their study. In contrast, Vuksanaj and Fisher reported that clearance (per kg body weight) in children aged 4–11 yr declined with age and body weight.[12] This apparent difference may be partly an artefact because of inclusion of extremely obese children, in particular in the age range 9–11 yr, resulting in an apparently small value for weight-normalized clearance. Over the range 5–8 yr, or 18–25 kg, which coincides with the age groups in the three studies, the differences between the studies are rather small (fig. 4). It is likely that weight-normalized clearance is maximal for children of 5–8 yr, or 18–25 kg, and declines with increasing age and body weight. This decline is likely to be related to declining body surface area/body weight ratio. Assuming a value of 4.0 ml $min^{-1}$ $kg^{-1}$ for clearance of a normal adult,[13] clearance normalized for body surface area is 150 ml $min^{-1}$ $m^{-2}$ for both adults and children.

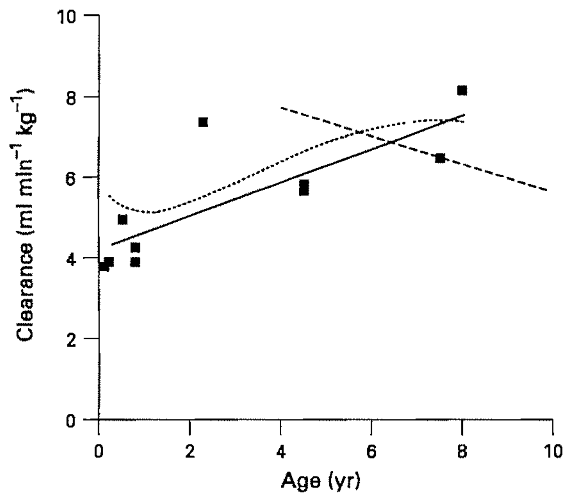

*Figure 4* Relationship between plasma clearance and age in infants and children (■). The solid line represents the regression line ($Cl_{pl}=0.40\times age+4.25$). The dotted line was calculated from the results of O'Kelly and colleagues (range 0.25–8 yr)[5] and the dashed line was calculated from the results of Vuksanaj and Fisher (range 4–11 yr).[12]

Figure 4 demonstrates that for children less than about 3 yr, clearance is lower than predicted from values of older children and adults. This lower clearance may reflect immaturity of the liver and kidneys, the main eliminating organs.[14]

We observed a negative correlation for weight-normalized volume of distribution at steady state and age and body weight. In contrast, O'Kelly and colleagues found that volume of distribution increased slightly with age and weight, [5] whereas Vuksanaj and Fisher did not find a significant trend in their study in children aged 4–11 yr.[12] One can only speculate on the reason for these differences. It is possible that the different methodologies in the three studies may have created the observed differences. Comparing our results with weight-normalized volume of distribution at steady state in adults (205 ml $kg^{-1}$),[13] it may be concluded that in children aged 4–8 yr, $V^{ss}$ is lower than in adults. In contrast, $V^{ss}$ in infants is higher than in adults and children. The distribution of quaternary compounds such as rocuronium and other neuromuscular blocking agents is limited to the extracellular fluid (ECF). During the first year of life, the volume of ECF decreases from 44% of body weight at birth to about 22% of body weight at 1 year, a value close to that in adults.[15] The higher percentage ECF predicts a higher $V^{ss}$ in infants compared with children and adults.

The larger plasma clearance and lower volume of distribution in children compared with both infants and adults resulted in a markedly lower mean residence time and a shorter duration of neuromuscular block. A short duration of action of an intubating dose of rocuronium has been observed in children compared with infants[2,16] and adults.[17]

Other non-depolarizing neuromuscular blocking agents do not seem to show similar correlations between pharmacokinetic variables and patient characteristics in children. All existing studies support the concept that the volume of distribution of a neuromuscular blocking agent is larger in infants than in children,[18–22] in accordance with the larger percentage of extracellular fluid. For plasma clearance the situation is different. Studies with atracurium revealed that plasma clearance is larger in infants than in children.[21,22] This may be explained by the organ-independent elimination rate in combination with the larger volume of distribution. A study with vecuronium showed similar plasma clearance in both age groups,[20] and studies with d-tubocurarine indicated that plasma clearance may be smaller in infants compared with children.[18,19] The latter finding may result from the relatively large contribution of renal clearance in elimination, compared with vecuronium.

### PHARMACOKINETIC–PHARMACODYNAMIC RELATIONSHIP

Our results showed that infants needed a lower concentration of rocuronium in the effect compartment than children in order to produce the same degree of neuromuscular block. This result corroborates data available for d-tubocurarine and vecuronium.[18–20] The lower effective concentrations in infants may be because of their potentially lower quantal content of acetylcholine, as shown in newborn rats, the larger incidence of single molecule block in infancy, and/or less protein binding as a result of low concentrations of plasma proteins in infants.[14 23 24] The slope of the concentration–response relationship based on the Hill equation was steeper in infants than in children. This finding supports the previous study of dose–response curves of rocuronium in infants, children and adults which showed the steepest slope in infants.[3] This steeper slope in infancy may be a unique characteristic of rocuronium as this phenomenon has not been seen with other neuromuscular blocking agents.[18 20 22]

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*British Journal of Anaesthesia* 1997; 78: 696–700

# Use of inhaled nitric oxide in British intensive therapy units

B. H. CUTHBERTSON, S. STOTT AND N. R. WEBSTER

## Summary

The use of inhaled nitric oxide in the critically ill has increased significantly over the past few years but little published information exists on standards for current practice. Sixty-four intensive therapy units in the UK were surveyed by questionnaire from which 54 (84.4%) satisfactory replies were received. We present the survey results and put forward recommendations based on current literature and our own clinical experience for the safe use of inhaled nitric oxide. (*Br. J. Anaesth.* 1997; **78**: 696–700).

**Key words**
Gases non-anaesthetic. Pharmacology, nitric oxide. Anaesthesia, audit. Intensive care, audit.

The use of inhaled nitric oxide (NO) in intensive therapy units (ITU) in the UK has increased significantly over the past few years, despite the lack of evidence that it improves outcome.[1–4] There are currently no published recommendations for delivery, monitoring and scavenging of what is potentially a dangerous gas. In light of recent reports indicating the potential dangers of this therapy to both patients and staff,[5–8] we felt information was required on current British practice. In addition, we feel there is a need for recommendations regarding the safe administration and use of inhaled nitric oxide. We therefore sought to establish current practice of inhaled nitric oxide in the ITU and to compile recommendations for its safe use.

## Methods

Using the current Directory of Emergency and Special Care Units (1996), we phoned all adult, cardiac and paediatric ITU in the UK with more than four beds and spoke to either medical or senior nursing staff. Special care baby units were excluded. A postal questionnaire was sent to all units that used inhaled nitric oxide therapy (appendix 1). We asked about indications for its use and currently used methods of delivery, monitoring and scavenging in individual units. Units were also asked about the minimum level of monitoring that they considered satisfactory for its safe use.

## Results

Sixty-four units were identified and completed replies were received from 54 (84.4%) after two mailings. Of these, 35 were adult units with 10 performing cardiac surgery, another eight were mixed adult and paediatric ITU and 11 were paediatric ITU. Within these units there was a mean of 8.5 (range 2–22) general beds, 8.0 (1–22) paediatric beds and 8.0 (3–12) cardiac beds.

### INDICATIONS

The most frequent indications for the use of inhaled nitric oxide are shown in table 1. Other less frequent indications for its use included weaning from extracorporeal membrane oxygenation (two units), ventricular off-loading in cardiac failure (two) and bronchiolitis (one). Using the American–European consensus conference definitions (appendix 2),[9] we were able to establish the disease severity for which units introduce inhaled nitric oxide therapy into clinical management of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (table 2). Of the 54 units which replied, the mean period that these units had used inhaled nitric oxide was 2.1 (0.1–6.0) yr. Twenty-seven units (50.0%) were carrying out research into some aspect of inhaled nitric oxide therapy and five (9.3%) used inhaled nitric oxide only as part of a study.

*Table 1* Indications for use of inhaled nitric oxide therapy (%). ALI=acute lung injury, ARDS=acute resiratory distress syndrome

| Indications | Incidence (%) |
|---|---|
| ALI/ARDS | 91 |
| Pulmonary hypertension | 70 |
| Paediatric cardiac surgery | 24 |
| Cardiac surgery | 18 |
| Cardiac transplantation | 9 |
| Other | 17 |

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Accepted for publication: February 3, 1997.
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*Table 2* Severity of ALI/ARDS at introduction of inhaled nitric oxide therapy (%). ALI=acute lung injury, ARDS=acute resiratory distress syndrome, SRF=severe respiratory failure

| Severity | Incidence (%) |
|---|---|
| ALI | 26 |
| ARDS | 12 |
| SRF | 46 |
| Other | 16 |

DELIVERY AND MONITORING

Ten (18.5%) units used an inspiratory injection system which injects nitric oxide into the inspiratory limb only during the inspiratory phase of the ventilator cycle; 52 (96.3%) used a continuous flow system and eight (14.8%) used both systems. To monitor delivery of inhaled nitric oxide, eight (15.9%) units used only chemiluminescent monitoring, 48 (90.6%) units used an electrochemical monitor, and eight (15.1%) units used both systems. Two (3.8%) units monitored expired nitrogen dioxide concentrations while six (11.3%) units measured environmental nitrogen dioxide. Two (3.8%) units did not monitor the concentration of inhaled nitric oxide.

Regarding minimum monitoring standards for the safe use of inhaled nitric oxide, eight (15.1%) units believed that inspiratory chemiluminescence monitoring of nitric oxide and nitrogen dioxide was required, whereas 45 (84.9%) thought that inspiratory electrochemical monitoring of nitric oxide and nitrogen dioxide was adequate. In addition to inspiratory monitoring, 22 (41.5%) units stated that expiratory monitoring should also be used. Three (5.9%) of these stated that a chemiluminescence analyser was necessary and 19 (35.8%) thought that electrochemical monitoring was sufficient. Only nine (16.9%) units felt that environmental nitrogen dioxide monitoring was necessary. Comparison between actual use of monitoring and what the surveyed units stated to be minimum monitoring standards is shown in table 3. Methaemoglobin concentrations were measured daily in 27 (54%) units; in 16 (32.0%) it was measured with every blood-gas analysis but in seven (14.0%) units it was not measured. Four (7.6%) units said that although they measured methaemoglobin concentrations they did not feel it was necessary.

*Table 3* Current use of monitoring compared with surveyed units stated minimum monitoring standards

| | Current monitoring (%) | Stated minimum standard (%) |
|---|---|---|
| Inspiratory chemiluminescence monitoring | 16 | 15 |
| Inspiratory electrochemical monitoring | 91 | 85 |
| Expiratory monitoring | 4 | 42 |
| Environmental monitoring | 11 | 17 |

SCAVENGING

Table 4 shows the different methods of scavenging. Of the units using filtration systems, three (5.8%) units used the ABEK HgCONO-P3 filter, five (9.6%) units used charcoal absorbers and four (7.7%) units used soda lime.

*Table 4* Use of scavenging systems with inhaled nitric oxide therapy

| Type of scavenging used | Incidence (%) |
|---|---|
| Passive | 19 |
| Filtration | 23 |
| Active | 23 |
| None | 40 |

## Discussion

The potential benefits of nitric oxide are attractive to improve oxygenation and reduce pulmonary artery pressures in ARDS and act as a pulmonary artery vasodilator in pulmonary artery hypertension without systemic effects. As yet, these benefits are not proved in terms of patient outcome and thus therapy should still be thought of as experimental. We found that 50% of the units currently using inhaled nitric oxide were carrying out research in this area and thus nitric oxide is being used widely in research designs. Only 9.4% of responding units were using it solely for research purposes. Until the risk/benefit ratio has been established it would seem logical to use inhaled nitric oxide therapy in more severely ill critical care patients. No evidence is yet available to allow recommendations to be made for the introduction of inhaled nitric oxide. Our opinion is that in ARDS, ventilation should be optimized with an arbitrary partial pressure of arterial oxygen to fractional inspired oxygen concentration ratio ($Pa_{O_2}:FI_{O_2}$) of less than 14 kPa (106 mm Hg) before introduction of inhaled nitric oxide for clinical purposes.

DELIVERY

There are essentially two ways to deliver inhaled nitric oxide, either continuously or by intermittent flow. The gold standard for nitric oxide delivery is a Servo controlled inspiratory injection device such as the NODOMO system (Dräger Medical UK, Hemel Hemstead, Herts, UK) which allows injection of nitric oxide into the inspiratory limb of the system during inspiration only. This technique reduces the bolus effect seen with continuous flow systems and reduces nitrogen dioxide formation because of decreased nitric oxide and oxygen mixing time.[9 10] The continuous flow system uses a calibrated flowmeter delivering a continuous flow of nitric oxide–nitrogen 10–800 ml min$^{-1}$ throughout the respiratory cycle.[9] Medical quality nitric oxide–nitrogen is available in cylinders for direct patient use or can be delivered through stainless steel medical gas piping. Medical quality nitric oxide–nitrogen gas cylinders with a stainless steel pressure regulator, connectors and calibrated stainless steel flowmeter needle valves are the minimum required for the safe delivery of inhaled nitric oxide. Polytetrafluroethylene (PTFE) tubing for the delivery of inhaled nitric oxide is safe (personal communication, Nigel Wadsworth, BOC Special Gases, Guildford, Surrey). Cylinders of nitric oxide–nitrogen are available in 10- and 40-litre sizes and must be secured in the ITU so as to avoid injury. Methods of delivery for inhaled nitric oxide in the UK vary but the majority (96.3%) use nitric oxide cylinders and a continuous flow system. Some units did not monitor the delivery of nitric oxide; we would strongly discourage this practice.

### MONITORING

Nitric oxide in gas mixtures can be measured either with chemiluminescence or electrochemical analysers. Electrochemical analysers monitor both nitric oxide and nitrogen dioxide concentrations to an accuracy of at least 1 part per million (ppm) while chemiluminescence analysers monitor nitric oxide, nitrogen dioxide and other higher oxides of nitrogen to an accuracy of a few parts per billion. When placed at the distal end of the inspiratory limb, nitric oxide and nitrogen dioxide monitors provide information on the delivered dose of nitric oxide to the patient and information on the formation and delivery of the potentially toxic nitrogen dioxide. Few clinical indications require delivery of greater than 80 ppm of inhaled nitric oxide and this should be regarded as a maximum dose,[2 3 10 12] but it should be noted that the Control of Substances Hazardous to Health (COSHH) guidelines for inspired nitric oxide concentrations are 25 ppm over an 8-h time-weighted average (TWA) and 35 ppm over a 15-min TWA. Maximum nitrogen dioxide concentrations should be less than 3 ppm over an 8-h TWA and 5 ppm over a 15-min TWA.[12] There is evidence that concentrations as low as 5 ppm of nitrogen dioxide cause surfactant damage in rats.[13 14] Nitrogen dioxide monitoring in the expiratory limb of the system provides some information on the amount of nitrogen dioxide being exhausted from the system but this does not reflect environmental nitrogen dioxide concentrations.[15–17] We recommend that inspiratory electrochemical or chemiluminescence monitoring of nitric oxide and nitrogen dioxide is the minimum requirement. Expiratory monitoring of nitrogen dioxide does not provide any useful information on atmospheric nitrogen dioxide concentrations and thus we do not feel its measurement is routinely required.

Environmental nitric oxide and nitrogen dioxide monitoring in the ITU can be performed using chemiluminescence or electrochemical analysers at the patient bedside. Environmental nitric oxide concentrations should not exceed the COSHH guidelines, but concentrations of 1 ppm of nitric oxide are the highest recorded in a clinical environment during the use of inhaled NO.[10 15] In light of the current published data, environmental nitric oxide and nitrogen dioxide monitoring is not routinely required.

The reaction of nitric oxide with haemoglobin produces the compound methaemoglobin. Doses of nitric oxide far greater than those used clinically do not cause significant methaemoglobinaemia in adults.[18] To date there are only two case reports of significant methaemoglobinaemia during inhaled nitric oxide therapy. Both were in babies and in one case there was an overdose of nitric oxide.[19 20] Inhaled nitric oxide has now been used in many thousands of patients without further reports of methaemoglobinaemia. We suggest that methaemoglobin measurements may be unnecessary, but until further evidence is available they should be measured daily.

A surprisingly high percentage (41.5%) of respondents thought that expired nitrogen dioxide monitoring was a minimum requirement but there is no current evidence to support this practice. Otherwise, the minimum monitoring standards from the surveyed units broadly agreed with our recommendations for inspiratory nitric oxide and nitrogen dioxide and daily methaemoglobin measurement being the minimum requirement. Although we do not feel that exhaled or environmental nitrogen dioxide measurements are required, we would not discourage this safety orientated approach. Environmental electrochemical nitrogen dioxide monitors are now readily available at an affordable price.

### SCAVENGING

Scavenging can be used both in the inspiratory limb of the system to scavenge inspired nitrogen dioxide or on the expiratory limb to scavenge expired nitric oxide and nitrogen dioxide. Active scavenging systems would be the gold standard for nitric oxide and nitrogen dioxide scavenging, but are expensive and are not commonly available in the ITU. Active scavenging can also affect the performance of the expiratory valve of the ventilator. Because of the high moisture content of both inspired and expired gases, passive scavenging, which usually involves a length of hose being placed out of a window, is often associated with excess moisture collection in the tubing. Expiratory scavenging of nitric oxide or nitrogen dioxide with soda lime has been reported to be ineffective and although soda lime containing potassium permanganate indicator has been shown to scavenge inspired nitric oxide and nitrogen dioxide, this was probably because of the reaction of the indictor and not the soda lime.[21 22] Two stage permanganate and charcoal filtration devices are also available but there is no clinical evidence regarding efficiency. The lack of evidence for effectiveness of soda lime in expiratory scavenging implies that we are unable to recommend its clinical use at this time. Charcoal type absorbers are ineffective absorbers of nitric oxide or nitrogen dioxide.[21] The ABEK HgCONO-P3 filter (Dräger Industrial Ltd., Hemel Hempstead, Herts, UK) which is used industrially appears to scavenge nitric oxide and nitrogen dioxide effectively.[21]

More than half (59.6%) of responding units used some type of scavenging system. Health Technical Memorandum 2025 states that in units with adequate ventilation in clinical areas (10–12 air changes per hour), scavenging of nitric oxide or nitrogen dioxide is not necessary but recommends scavenging in units that do not reach this standard.[21 23] Expiratory scavenging using the ABEK HgCONO-P3 filter, active or passive scavenging are appropriate in units that do not meet the above guidelines. We would not discourage the practice of scavenging exhaled nitric oxide and nitrogen dioxide and would recommend scavenging in poorly ventilated units. It should be noted that there is little evidence to support the use of soda lime or charcoal absorbers in the scavenging of exhaled nitric oxide and nitrogen dioxide.

In summary, inhaled nitric oxide is a new form of therapy in the ITU. The use of this potentially toxic compound should be supervised closely by experienced clinicians and its delivery and monitoring standardized to acceptable minimum levels. At present there is wide variety in the standards of clinical practice for using inhaled nitric oxide in the UK. We have put forward recommendations (appendix 3) for its use with the belief that this will promote discussion and research into nitric oxide therapy and with the hope that national guidelines may soon become available.

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## Appendix 1

SURVEY OF THE USE OF INHALED NITRIC OXIDE IN THE ITU

Unit number ________________

Dear Colleague

We believe that your unit uses inhaled nitric oxide therapy. As you are probably aware there has been concern stated by the CSM on the use of inhaled NO in clinical practice. We are conducting a postal survey of all the units in the UK that use inhaled NO. We would appreciate if you could complete this short questionnaire and return it to us in the enclosed STA as soon as it is convenient.

Thank you for your help.

Brian H Cuthbertson and Steve Stott, Intensive Care Unit, Aberdeen Royal Infirmary, Aberdeen.

**A.**

Name of unit ________________

Name of person filling in questionnaire ________________

Grade ________________

Bed number:- total___ general___ paediatric___ cardiac___

**B.** How long have you used it:- ____ years____ months

What indications do you use inhaled NO for in your hospital:-

a. ALI/ARDS ☐
b. Secondary pulmonary hypertension ☐
c. Pulmonary vasodilator during adult cardiac surgery ☐
d. Cardiac transplant surgery ☐
e. Paediatric cardiac surgery ☐
f. RDS of the newborn ☐
g. Others -please state ________________

If you use inhaled NO for ALI/ARDS, what criteria do you use for its use? (American–European consensus conference definitions).

a. Consensus conference definition for ALI ☐
($Pa_{O_2}/FI_{O_2}$ ratio <300 mm Hg, infiltrates on CXR, PCWP <18 mm Hg)

b. Consensus conference definition for ARDS ☐
($Pa_{O_2}/FI_{O_2}$ ratio <200 mm Hg, infiltrates on CXR, PCWP < 18 mm Hg)

c. Severe respiratory failure (ECMO) criteria ☐
($Pa_{O_2}$ <8 kPa on $FI_{O_2}$ 1.0 for >8 h)

d. Other (please state) ________________

Are you undertaking research in the subject of inhaled NO:- Yes / No

Are you using inhaled NO only as part of a trial:- Yes / No

What equipment do you use for *administration* of inhaled NO ________________

What equipment do you use for *measurement* of inhaled NO levels ________________

What monitoring do you feel is the minimum necessary for the safe use of inhaled NO:-

a. Inspired NO and $NO_2$ levels:-
  chemiluminescent monitor ☐
  electrochemical monitor ☐
b. Expired NO and $NO_2$ levels -
  chemiluminescent monitor ☐
  electrochemical monitor ☐
c. Methaemoglobin levels:- Daily ☐ Every gas ☐ Not required ☐
d. Other (please state) ________________

What means of scavenging of NO do you use:- None ☐
Passive ☐
Active ☐
Soda lime ☐
Other ☐

Thank you for your time

## Appendix 2

AMERICAN–EUROPEAN CONSENSUS CONFERENCE DEFINITION FOR ALI AND ARDS AND THE SEVERE RESPIRATORY FAILURE CRITERIA

Abbreviations: ECMO=extracorporeal membrane oxygenation, PCWP=pulmonary capillary wedge pressure, CXR=chest x-ray.

| | |
|---|---|
| Acute lung injury (ALI) | $Pa_{O_2}/FI_{O_2}$ ratio <39.5 kPa (300 mm Hg)<br>Bilateral infiltrates on CXR<br>PCWP <18 mm Hg |
| Acute respiratory distress syndrome (ARDS) | $Pa_{O_2}/FI_{O_2}$ ratio <26.3 kPa (200 mm Hg)<br>Bilateral infiltrates on CXR<br>PCWP <18 mm Hg |
| Severe respiratory failure criteria | $Pa_{O_2}/FI_{O_2}$ ratio <8 kPa (60.8 mm Hg) for >8 h |

## Appendix 3

RECOMMENDATIONS FOR THE USE OF INHALED NITRIC OXIDE IN THE ITU

Abbreviations: NO=nitric oxide, $NO_2$=nitrogen dioxide, PTFE=polytetrafluroethylene, COSHH=Care of Substances Hazardous to Health, ppm= parts per million, TWA=time-weighted average.

*Table A1* Recommendations for the use of inhaled nitric oxide in the ITU

| | |
|---|---|
| Delivery | 1. Medical NO/$N_2$ gas mixture<br>2. Stainless steel pressure regulators, connectors and flowmeter needle valves<br>3. Calibrated flowmeter<br>4. Stainless steel/PTFE tubing |
| Monitoring | 1. Inspiratory NO and $NO_2$<br>2. Chemiluminescence or electrochemical monitor<br>3. Daily methaemoglobin concentrations |
| Exposure | 1. Maximum inhaled NO <80 ppm<br>2. Maximum inhaled $NO_2$ <3 ppm<br>3. Maximum environmental NO <25 ppm for 8 h TWA<br>4. Maximum environmental $NO_2$ <3 ppm for 8 h TWA |
| Scavenging | 1. Not required in well ventilated unit<br>2. Required in units with less than 10–12 air changes per hour |
| Scavenging techniques | 1. ABEK HgCONO-P3 filter<br>2. Active scavenging<br>3. Passive scavenging |

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# Comparison of the effects of ketamine–midazolam with those of fentanyl–midazolam on cortical somatosensory evoked potentials during major spine surgery†

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## Summary

Cortical somatosensory evoked potentials (CSEP) allow monitoring of spinal cord function during surgery. Ketamine has been shown to enhance CSEP amplitude, but there is no previous study comparing its effects with those of other anaesthetic regimens. Therefore, we have compared the effects of ketamine with those of fentanyl, both combined with midazolam, on CSEP monitoring during major spine surgery. Twenty patients with normal preoperative CSEP were allocated randomly to a ketamine or fentanyl group. Anaesthesia was induced with ketamine 3 mg kg$^{-1}$ or fentanyl 6 µg kg$^{-1}$ i.v., and midazolam 0.3 mg kg$^{-1}$ i.v in both groups, and maintained with continuous i.v infusion of ketamine 2 mg kg$^{-1}$ h$^{-1}$ or fentanyl 3 µg kg$^{-1}$ h$^{-1}$, combined in both groups with midazolam 0.15 mg kg$^{-1}$ h$^{-1}$ and 60% nitrous oxide in oxygen. CSEP were elicited by tibial posterior nerve stimulation and measured P1 and N1 latencies, and P1-N1 amplitude. CSEP were recorded before and after induction, at 15 min, 1 and 2 h after induction, during skin closure and after removal of nitrous oxide. Both groups were comparable in characteristics, duration of surgery, mean arterial pressure and temperature. CSEP latencies were not significantly affected in either group. CSEP amplitude decreased significantly over time in the fentanyl group (from mean 2.02 (SEM 0.41) to 0.95 (0.17) µV, $P<0.05$), but not in the ketamine group (from 1.33 (0.36) to 1.05 (0.31) µV, ns). Nevertheless, we did not observe any significant differences in amplitudes or latencies between the two groups. The delay in obtaining the first voluntary postoperative motor response was significantly greater in the ketamine group (170 (54) *vs* 55 (17) min, $P<0.01$). Both ketamine and fentanyl allowed us to obtain reliable CSEP during major spine surgery, and there were no significant difference between these two anaesthetic regimens for CSEP monitoring, but a longer delay for voluntary postoperative motor assessment was observed in the ketamine group. (*Br. J. Anaesth.* 1997; **78**: 701–706).

**Key words**
Brain, evoked potentials. Anaesthetics i.v., ketamine. Analgesics opioid, fentanyl. Hypnotics benzodiazepine, midazolam. Surgery, spinal.

Cortical somatosensory evoked potentials (CSEP) assess neural transmission in afferent spinal cord pathways and are used to monitor spinal cord function during spine surgery to prevent neurological injury.[1,2] However, changes in CSEP may result from surgical stimulation,[3,4] anaesthetic agents[5–8] or haemodynamic instability.[1,9] Consequently, to improve CSEP recording and increase their reliability, the anaesthetic technique should minimize its effects on amplitudes and latencies of CSEP, and provide haemodynamic stability.

Previous studies have reported that fentanyl[3,5,7,10] and midazolam[7] induce modest alterations in CSEP amplitudes and latencies enabling appropriate monitoring of CSEP signals. Moreover, the combination of fentanyl and midazolam provides haemodynamic stability. Ketamine has been shown to enhance CSEP amplitude and has therefore been suggested as a useful anaesthetic agent when CSEP are required, enabling more reliable intraoperative spinal cord function monitoring.[11] However, this study was not performed during spine surgery, did not assess the effects of ketamine over a long period and did not compare ketamine with another anaesthetic agent. Thus our prospective, randomized study was undertaken to compare the effects of ketamine–midazolam with fentanyl–midazolam anaesthesia on CSEP monitoring during major spine surgery.

## Patients and methods

After obtaining approval from the local Ethics Committee and informed consent, we studied 20 consecutive ASA I–II patients undergoing major spine surgery (scoliosis or spinal fusion). Patients

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with abnormal preoperative CSEP were excluded; additional criteria for exclusion were hypertension, coronary artery disease, psychiatric disorders and ASA III or IV status.

### ANAESTHESIA TECHNIQUE

Patients received hydroxyzine 1–1.5 mg kg$^{-1}$ orally 90 min before surgery. Using a random number table, patients were allocated to a ketamine or fentanyl group. Anaesthesia was induced with ketamine 3 mg kg$^{-1}$ or fentanyl 6 μg kg$^{-1}$ i.v., combined with midazolam 0.3 mg kg$^{-1}$ i.v in both groups. Neuromuscular block for tracheal intubation was produced with vecuronium 0.1 mg kg$^{-1}$ i.v. Anaesthesia was maintained with continuous i.v. infusion of ketamine 2 mg kg$^{-1}$ h$^{-1}$ or fentanyl 3 μg kg$^{-1}$ h$^{-1}$, combined with midazolam 0.15 mg kg$^{-1}$ h$^{-1}$ and 60% nitrous oxide in oxygen in both groups. After skin closure, nitrous oxide was first removed and after the last CSEP measurement the infusions were discontinued.

Throughout the study the lungs were ventilated mechanically and minute ventilation was adjusted to maintain end-tidal carbon dioxide tension ($E'_{CO_2}$) at 4.0–4.8 kPa. Oesophageal temperature was monitored, and hypothermia was prevented using a heating blanket and perfusion warming. Haemodynamic measurements were obtained via an indwelling radial artery catheter connected to a haemodynamic monitor (HP 78354, Hewlett-Packard, Andover, MA, USA). When required, an i.v. bolus of nicardipine 2 mg (Loxen, Sandoz) was administered to maintain mean arterial pressure (MAP) at 60–80 mm Hg to decrease intraoperative bleeding. Haemoglobin concentration was measured during operation using an infrared monitor (HemoCue, Angelholm, Sweden) and was maintained greater than 8 g dl$^{-1}$ using autologous and homologous blood transfusion, as available.

### CSEP RECORDING

CSEP were recorded with a Nicolet compact IV (Nicolet Biomedical Instruments, Madison, WI, USA) and were elicited by alternate right and left tibial posterior nerve stimulation with subdermal needle electrodes placed on the ankle (frequency 4.3 Hz, duration 150 ms, intensity twice the motor threshold). As regional hypothermia could affect CSEP,[12] we paid careful attention to covering the lower limbs with a heating blanket. CSEP were recorded simultaneously with transcutaneous scalp Ag–AgCl electrodes (impedance<2 kΩ) located in the medio-central and medio-frontal positions ($C_Z$-$F_Z$ in the International 10-20 System).[1] To obtain a better CSEP signal, 500 stimulations were cumulated and averaged every 2 min, using bandpass filters of 10 and 1000 Hz and recorded over a 100-ms time base. At each sample period, CSEP measurements were obtained by averaging duplicate tracings. During diathermy, CSEP acquisition was halted automatically. According to the nomenclature of the cortical peaks of tibial nerve evoked potentials described by Nuwer[13] and Stöhr,[14] positive waves of the CSEP are represented by downward deflections and labelled P (fig. 1). In the same way, negative waves of the CSEP are represented by upward deflections and labelled N (fig. 1). Latencies were measured regarding positivity at approximately 40 ms (P1) and negativity at approximately 50 ms (N1) of the primary cortical peaks from the time of stimulus. Amplitude (A) was measured from peak to peak of these two deflections (fig. 1). CSEP monitoring was recorded continuously by a trained neurophysiologist who was unaware of the anaesthesia technique used. Intraoperative abnormalities of CSEP were defined as an increase in latency (P1 or N1) of at least 10% of previous values (throughout two acquisition periods, 4 min) and a decrease in amplitude of at least 50% of previous values, as reported previously.[1 2 6] According to our routine procedure and as recommended previously,[2] a "wake-up" test[15] was required if such abnormalities occurred during a high-risk period of surgery.

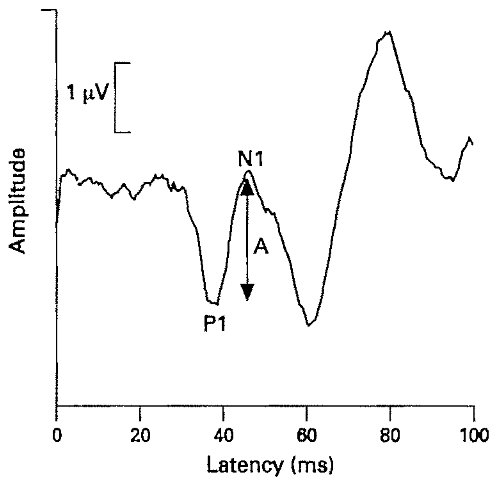

*Figure 1* Typical tracing of cortical somatosensory evoked potentials after tibial posterior stimulation. P1 = first positive deflection occuring at approximately 40 ms from the time of stimulus, N1 = first negative deflection occuring at approximately 50 ms from the time of stimulus. Amplitude (A) was measured from peak to peak of these two deflections.

### MEASUREMENTS

The following variables were measured simultaneously while patients were awake (control period), at the end of induction, 15 min, 1 and 2 h after induction, during skin closure and after removal of nitrous oxide (expired concentration ($E'_{N_2O}$) less than 10%) : heart rate (HR), MAP, $E'_{CO_2}$, $E'_{N_2O}$, oesophageal temperature and CSEP. Before and after induction, at the end of surgery and in the recovery room, arterial blood was obtained to measure partial pressure of oxygen ($Pa_{O_2}$) (BGElectrolytes Apparatus, Instrumentation Laboratory, Milano, Italy) and haemoglobin concentration (Cobas Argo, Apparatus, Roche, Basle, Switzerland). We also recorded the amount of crystalloids, colloids and blood administered during operation, duration of anaesthesia and surgery, and delay between the end of anaesthesia and the first voluntary postoperative motor response of the lower limbs. To obtain a reliable voluntary motor response of the lower limbs, this test was explained to each patient during the preoperative visit, and the postoperative assessment was performed every 15 min in the recovery room by a physician who was unaware of the anaesthesia technique.

### STATISTICAL ANALYSIS

Data are expressed as mean (SEM). Comparisons of two means and two percentages were performed using the Student's *t* test and Fisher's exact method, respectively. Comparison of several means was performed using repeated-measure analysis of variance and Newman–Keuls test. All *P* values were two-tailed and $P<0.05$ was considered significant. Statistical analysis was performed on a computer using PCSM software (Deltasoft, Meylan, France).

## Results

CSEP recording was available and satisfactorily analysed in all patients throughout the study. We did not have to perform a wake-up test, and no neurological complications occurred during or after surgery. We did not observe any undesirable psychomimetic side effects related to ketamine. There were no significant differences between the two groups in age, ASA status, body weight, duration of anaesthesia or surgery, total dose of nicardipine, intraoperative fluids or blood transfusion (table 1). HR was significantly greater in the ketamine group, but MAP, temperature, $E'_{CO_2}$, $Pa_{O_2}$ and haemoglobin concentration were not significantly different between the two groups (table 2).

CSEP amplitude decreased significantly from induction until the end of surgery in comparison with control values in the fentanyl group (from 2.02 (0.41) to 0.95 (0.17) µV, $P<0.05$), but not in the ketamine group (from 1.33 (0.36) to 1.05 (0.31) µV, ns). However, there were no significant differences between the two groups (fig. 2). In both groups, we observed no significant increases in CSEP amplitude at the end of surgery after removal of nitrous oxide and there were no significant differences between groups (fig. 2).

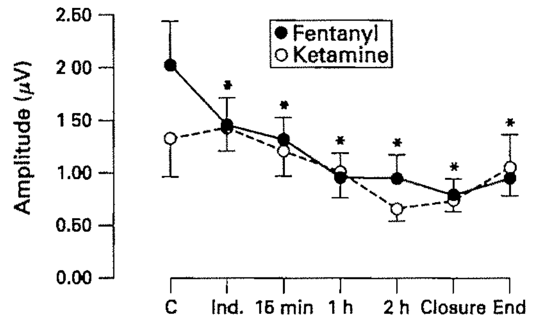

*Figure 2* Comparison of amplitude of cortical somatosensory evoked potentials in the ketamine ($n=10$) and fentanyl ($n=10$) groups when awake (control (C)), immediately after induction of anaesthesia (Ind.), at 15 min, 1 and 2 h of anaesthesia, during skin closure (Closure) and at the end of anaesthesia with removal of nitrous oxide (i.e. end-tidal nitrous oxide <10%) (End). Data are mean (SEM). $^*P<0.05$ *vs* control values. *P* values refer to between-group differences.

*Table 1* Comparison of the main characteristics in the ketamine and fentanyl groups. Data are mean (SEM or range or number). No significant difference between groups

| | Ketamine group ($n=10$) | Fentanyl group ($n=10$) |
|---|---|---|
| Age (yr) | 53 (22–83) | 49 (31–64) |
| Sex (M/F) | 7/3 | 2/8 |
| ASA status (I/II) | 6/4 | 7/3 |
| Body weight (kg) | 64 (3) | 60 (4) |
| Duration of anaesthesia (min) | 291 (21) | 310 (20) |
| Duration of surgery (min) | 221 (16) | 204 (27) |
| Intraoperative crystalloids (ml) | 3050 (328) | 3050 (189) |
| Intraoperative colloids (ml) | 650 (130) | 425 (167) |
| Intraoperative blood transfusion (ml) | 780 (323) | 870 (343) |
| Total dose of nicardipine (mg) | 10 (3) | 11 (4) |

*Table 2* Comparison of heart rate (HR), mean arterial pressure (MAP), oesophageal temperature, end-tidal $CO_2$ concentration ($E'_{CO_2}$), and partial arterial oxygen pressure ($Pa_{O_2}$) in the ketamine ($n=10$) and fentanyl ($n=10$) groups. Data are mean (SEM). $^*P<0.05$ *vs* control values; $^\dagger P<0.05$ *vs* induction values

| | Group | Control | Induction | 15 min | 1 h | 2 h | Skin closure | End | Comparison between groups |
|---|---|---|---|---|---|---|---|---|---|
| HR (beat $min^{-1}$) | Ketamine | 89 (4) | 93 (5) | 90 (4) | 80 (6) | 80 (5) | 78 (4) | 76 (4)* | $P<0.05$ |
| | Fentanyl | 88 (5) | 77 (6) | 69 (5)* | 67 (3)* | 70 (7)* | 84 (8) | 81 (9) | |
| MAP (mm Hg) | Ketamine | 103 (3) | 99 (13) | 95 (4) | 91 (5) | 80 (4)* | 77 (4)* | 78 (4)* | ns |
| | Fentanyl | 99 (4) | 84 (5)* | 82 (9)* | 79 (5)* | 74 (4)* | 77 (4)* | 74 (4)* | |
| Temperature (°C) | Ketamine | 36.8 (0.1) | 36.2 (0.2)* | 35.9 (0.2)* | 35.2 (0.2)* | 35.2 (0.2)* | 35.3 (0.3)* | 35.3 (0.3)* | ns |
| | Fentanyl | 37.0 (0.1) | 36.3 (0.2)* | 36.1 (0.2)* | 35.6 (0.2)* | 35.4 (0.2)* | 35.4 (0.4)* | 35.4 (0.4)* | |
| $E'_{CO_2}$ (kPa) | Ketamine | — | 4.5 (0.4) | 4.4 (0.3) | 3.9 (0.1)† | 3.9 (0.4)† | 3.7 (0.1)† | 3.6 (0.1)† | ns |
| | Fentanyl | — | 4.3 (0.3) | 4.1 (0.1) | 3.9 (0.1) | 4.0 (0.1) | 3.9 (0.1) | 3.6 (0.1)† | |
| $Pa_{O_2}$ (kPa) | Ketamine | — | 216 (17) | — | — | — | — | 203 (28) | ns |
| | Fentanyl | — | 217 (20) | — | — | — | — | 218 (43) | |
| Haemoglobin (g $dl^{-1}$) | Ketamine | — | 11.0 (0.5) | — | — | — | — | 8.9 (0.7)† | ns |
| | Fentanyl | — | 9.8 (0.2) | — | — | — | — | 8 0 (0.3)† | |

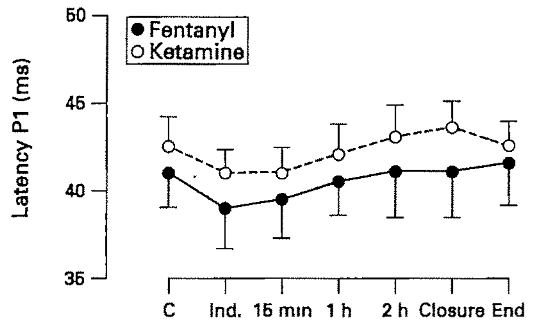

*Figure 3* Comparison of P1 latency of cortical somatosensory evoked potentials in the ketamine ($n$=10) and fentanyl ($n$=10) groups when awake (control (C)), immediately after induction of anaesthesia (Ind.), at 15 min, 1 and 2 h of anaesthesia, during skin closure (Closure) and at the end of anaesthesia with removal of nitrous oxide (i.e end-tidal nitrous oxide <10%) (End). Data are mean (SEM). No significant differences between groups.

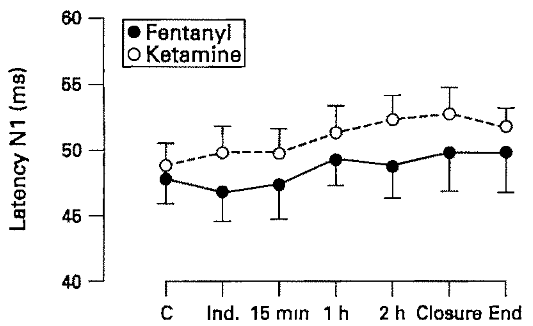

*Figure 4* Comparison of N1 latency of cortical somatosensory evoked potentials in the ketamine ($n$=10) and fentanyl ($n$=10) groups when awake (control (C)), immediately after induction of anaesthesia (Ind.), at 15 min, 1 and 2 h of anaesthesia, during skin closure (Closure) and at the end of anaesthesia with removal of nitrous oxide (i.e end-tidal nitrous oxide <10%) (End). Data are mean (SEM). No significant differences between groups.

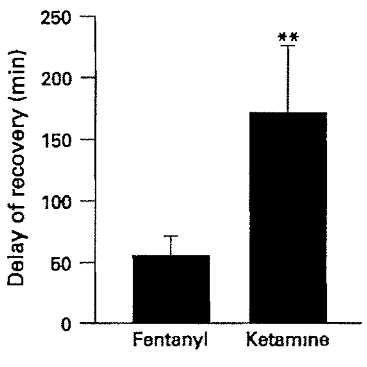

*Figure 5* Delay of recovery assessed by the first motor response obtained during the postoperative period in the ketamine ($n$=10) and fentanyl ($n$=10) groups. Data are mean (SEM). $^{**}P<0.01$ *vs* fentanyl group.

Latencies of P1 (fig. 3) and N1 (fig. 4) remained unchanged in each group throughout the study, including during removal of nitrous oxide. There were no significant differences in latencies between the two groups (figs 3, 4).

We observed a significantly longer delay of recovery, assessed by the first voluntary motor response, in the ketamine group compared with the fentanyl group (fig. 5).

## Discussion

We found that both ketamine–midazolam and fentanyl–midazolam anaesthesia, with 60% nitrous oxide in oxygen, enabled us to obtain satisfactory CSEP recordings, and we did not observe any significant differences in latencies and amplitudes of CSEP between the two groups. In contrast, recovery was delayed significantly in the ketamine group.

During spine surgery, CSEP monitoring provides sensitive information on spinal cord dysfunction caused by mechanical spinal cord injury, ischaemia, or both.[1 2 9] In a large multicentre survey, including 51 263 procedures for major spine surgery, Nuwer and colleagues[2] reported that neurological deficits occurred in only 0.55% of patients when CSEP monitoring was performed. To increase the reliability of CSEP recording and monitoring, several independent technical factors should be controlled to decrease false positive and negative rates of spinal injury. First, experience in CSEP monitoring is an important factor, as reported previously.[1 2 16] In our study, CSEP monitoring was performed by the same neurophysiologist (F. L.) highly trained in intraoperative CSEP monitoring.[17 18] Second, the early cortical components, P1 and N1, are considered the most reliable waveforms for CSEP recording[1 19] because their amplitude is greater than that of other peaks and because they exhibit lower variability.[6] Indeed, P1 and N1 components usually exhibit variability less than 30% in amplitude and 1.0 ms in latency.[16] Consequently, in our study, P1 and N1 were analysed to obtain a better signal-to-noise ratio and to increase the reliability of our CSEP recordings. Third, factors other than the anaesthesia technique can affect CSEP recording. These factors are related to spinal cord ischaemia, profound and sustained systemic hypotension,[9 20] severe hypoxia[21] and low packed cell volume with hypovolaemic status.[1 20] In contrast, isovolaemic haemodilution in subjects with normal CSEP, as in our study, does not affect CSEP monitoring.[22] Impairment of CSEP monitoring may be related (mainly latencies rather than amplitudes) to hypothermia in the 25–35 °C temperature range,[23–25] hypocapnia[25 26] and hypercapnia.[25] We controlled all of these factors during surgery, including regional limb hypothermia. However, we recorded oesophageal temperature which correlates better with CSEP changes than lower limb muscle temperature.[24] Thus MAP, oesophageal temperature, $E'_{CO_2}$, $Pa_{O_2}$ and haemoglobin concentration were maintained within values which enabled CSEP to be monitored satisfactorily throughout the study (table 2). Moreover, there were no significant differences between the two groups for each of these variables (table 2). Lastly, neuromuscular block was produced by vecuronium for tracheal intubation but was not maintained during the study. Neuromuscular block has not been shown to alter CSEP recording.[27]

CSEP may be affected by volatile or i.v. anaesthetics,[1 5–8] and by their mode of administration (bolus *vs* continuous).[1 7 10] To improve CSEP recording and signal-to-noise ratio, some authors have suggested previously that ketamine be used as a general anaesthetic to increase cortical amplitudes of CSEP produced by peripheral nerve stimulation.[11] In contrast with previous observations, CSEP amplitude in the ketamine group was not increased significantly in our study. This difference may be explained easily. In our study, CSEP monitoring was performed throughout surgery over a long period (more than 2 h) and not only during the first 60 min after induction. As reported previouly,[28] the time course of anaesthetic effects on CSEP may be prolonged and complex, and to avoid confusing transient CSEP changes with sustained changes, a prolonged study is required. Examination of the results from Schubert, Licina and Lineberry[11] shows that the increase in CSEP amplitude was significant only during the first 30 min, immediately after bolus injection of ketamine, and was no longer significant 60 min later in comparison with pre-induction values, with or without exposure to nitrous oxide. To avoid transient CSEP changes, we performed continuous administration of i.v. anaesthetics. Moreover, our results are in accordance with a recent study in humans[29] which reported that the amplitude of mid-latency auditory evoked potentials is maintained, and not increased, during ketamine anaesthesia, compared with pre-induction values. It should also be pointed out that CSEP were recorded from the upper and not from the lower limbs in the study of Schubert, Licina and Lineberry.[11] Moreover, as in the studies carried out by Schubert, Licina and Lineberry[11] and Schwender and colleagues,[29] we did not observe any significant changes in the latencies of P1 and N1 with ketamine, and no significant differences were noted for latencies between the two groups. In summary, there were no significant differences between ketamine–midazolam and fentanyl–midazolam anaesthesia for CSEP variables throughout the study.

The only significant difference between the two groups was a greater delay in obtaining the first voluntary motor response in the recovery room. This suggests that the diagnosis of potential spinal cord dysfunction in the immediate postoperative period should have been delayed. Indeed, rapid postoperative assessment of spinal cord function is important to detect: (1) spinal cord injury limited to motor pathways, thus not detected by CSEP; (2) delayed consequences of intraoperative spinal cord injury; and (3) postoperative spinal cord injury (haematoma). Moreover, because an antagonist of ketamine does not exist, we may speculate that an intraoperative wake-up test could have been easier and more rapid with fentanyl–midazolam anaesthesia than with ketamine–midazolam anaesthesia. This may also be important, because fewer neurological deficits occurred if a wake-up test was performed with CSEP monitoring.[2]

There are some limitations of this study. First, some patients scheduled for spine surgery may have abnormal preoperative CSEP. Because we studied patients with normal preoperative CSEP, further studies are thus required to assess the precise effects of ketamine in patients with abnormal preoperative CSEP. Second, the study included only 20 patients, and thus its power may have been too low to detect a significant difference. However, we considered that, if a significant difference does exist, then the magnitude of the difference between the two groups would not be clinically important.

In summary, both ketamine and fentanyl allowed satisfactory CSEP monitoring during major spine surgery, and we found no significant difference in CSEP monitoring between these two anaesthetic regimens. Nevertheless, ketamine was associated with a significant longer delay for first postoperative voluntary motor function assessment and would not allow a rapid peroperative wake-up test. Consequently, there appears to be at present no advantage in the use of ketamine during major spine surgery when CSEP monitoring is required.

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# Influence of 0.2 minimum alveolar concentration of enflurane on the ventilatory response to sustained hypoxia in humans

B. NAGYOVA, K. L. DORRINGTON, M. J. POULIN AND P. A. ROBBINS

**Summary**

To determine the influence of 0.2 minimum alveolar concentration (MAC) of enflurane on the time course of ventilation during sustained hypoxia, we studied 10 healthy adult volunteers with and without enflurane. The following design was used: end-tidal $P_{O_2}$ was maintained at 13.3 kPa for 8 min, at 6.7 kPa for 20 min and at 13.3 kPa for 8 min. End-tidal $P_{CO_2}$ was held constant throughout at 0.67 kPa above the subject's natural value. Control experiments were conducted with no hypoxia imposed. During the experiment subjects breathed via a mouthpiece from an automated gas mixing system which controlled end-tidal values. Enflurane reduced baseline (euoxic) ventilation from 20.9 (SEM 2.0) litre min$^{-1}$ to 10.1 (1.0) litre min$^{-1}$ (ANOVA, $P<0.001$). Enflurane reduced the acute ventilatory response to hypoxia (AHVR) from 20.1 (3.3) litre min$^{-1}$ to 5.0 (1.3) litre min$^{-1}$ (ANOVA, $P<0.01$), and the ventilatory off-response at cessation of hypoxia from 11.7 (2.4) litre min$^{-1}$ to 1.8 (0.5) litre min$^{-1}$ (ANOVA, $P<0.02$). There was no significant difference in hypoxic ventilatory decline (HVD) without and with enflurane (8.9 (2.4) litre min$^{-1}$ *vs* 5.5 (1.1) litre min$^{-1}$; ANOVA, ns). These results confirm that 0.2 MAC of enflurane suppressed the acute ventilatory response to hypoxia, but had no significant effect on the subsequent ventilatory decline during sustained hypoxia. (*Br. J. Anaesth.* 1997; **78**: 707–713).

**Key words**

Anaesthetics volatile, enflurane. Ventilation, hypoxic response. Hypoxia.

In humans the time course of ventilation during a period of sustained hypoxia lasting approximately 30 min is characterized by a rapid increase in ventilation over the first few minutes (the acute hypoxic ventilatory response (AHVR)) followed by a gradual decline in ventilation over approximately 20 min (the hypoxic ventilatory decline (HVD), often referred to in the American literature as "roll-off"). HVD cannot be attributed entirely to wash-out of carbon dioxide because the decline is still present even when no changes in arterial carbon dioxide partial pressure (an isocapnic exposure) are permitted to occur during hypoxic exposure.[1] At the relief of isocapnic hypoxia, ventilation usually returns rapidly to its baseline or pre-hypoxic value.

Knill, Manninen and Clement showed the marked depressant effect of sub-anaesthetic concentrations of volatile anaesthetics, including enflurane, on AHVR.[2] Their result has been confirmed by several other groups, including for 0.1 minimum alveolar concentration (MAC) of enflurane,[3] 0.1% inspired halothane,[4] 0.1 MAC and 0.22% (0.15 MAC) halothane.[5 6]

In contrast with the effects of volatile anaesthetics on AHVR, a similar depressant effect on the magnitude of the subsequent ventilatory decline, HVD, has generally not been found. Young, Drummond and Warren[4] and Dahan and colleagues[6] have shown no significant effect of sub-anaesthetic concentrations of halothane on HVD. For isoflurane, Temp, Henson and Ward were unable to show any significant effect of 0.1 MAC of isoflurane on either AHVR or HVD during sustained mildly hypercapnic (end-tidal $P_{CO_2}$ 0.13–0.27 kPa greater than subject's natural value) hypoxia in adults.[7 8] Similar results for HVD were reported by Foo and colleagues[9] for equivalent sub-anaesthetic doses of isoflurane. In our previous study we observed no significant reduction in the magnitude of HVD during 0.1 MAC of enflurane.[3]

The finding that AHVR can be greatly attenuated but HVD relatively unaffected is slightly surprising given that, in conscious humans, (i) the magnitude of HVD correlates with the magnitude of AHVR,[10] (ii) other factors that affect AHVR such as almitrine[11] and somatostatin[12] also alter HVD and (iii) in humans who have undergone peripheral chemodenervation, HVD is abolished together with AHVR.[13] It would appear from such results that both AHVR and HVD are determined by the sensitivity of the peripheral chemoreflex loop and functionally correlated. The usual rapid return of ventilation to its pre-hypoxic value after relief of hypoxia suggests that HVD is a direct measure of the decrease over time in chemoreflex sensitivity.

However, in cats, recent studies have shown considerable differences in the form of the ventilatory response to sustained hypoxia between the awake

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and anaesthetized state.[14-18] In awake cats, the form of the ventilatory response to sustained hypoxia is similar to that in awake humans described above. It is clearly asymmetric, with the rapid increase in ventilation at the onset of hypoxia being larger than the rapid decrease at the relief of hypoxia.[10 18 19] On the other hand, in anaesthetized cats, the form of this response is much more symmetric with little difference between the magnitudes of the responses at the onset and relief of hypoxia.[14] This results, at the relief of hypoxia, in a decrease in ventilation to below its pre-hypoxic value, sometimes approaching a period of apnoea.

In most human studies using low doses of anaesthetics the usual finding has been that the response remains asymmetric, with the decrease in ventilation at the relief of hypoxia being smaller than the increase in ventilation at the onset of hypoxia. However, one study by Dahan and colleagues using halothane reported a symmetric response.[6]

The purpose of this study was to determine if low doses of enflurane affect HVD, and to convert the form of the ventilatory response in conscious humans from an asymmetric to a symmetric form, in a manner consistent with the differences between awake and anaesthetized cats. In order to examine this without a likelihood of apnoea or near apnoea occurring after relief of hypoxia and an associated uncontrollable increase in end-tidal $P\text{CO}_2$, the initial ventilations have to be high enough to allow a symmetric off-transient to occur. The strategy of Khamnei and Robbins[19] of conducting the experiments under hypercapnic conditions was used to achieve this.

## Subjects and methods

We studied 10 healthy adult volunteers (aged 26.9 (20–51) yr). All subjects received a written and verbal description of the experiments before they gave their consent. None of the subjects was receiving medication at the time of study and all were asked to refrain from taking food for at least 6 h and drinks for 4 h before the experiments. During the experiments in which no enflurane was administered, subjects were asked to watch television. During experiments in which enflurane was administered subjects were asked to shut their eyes in a partially darkened quiet room. Our aim in reducing the stimulus during enflurane sedation was to achieve as great degree of sedation as possible for the dose of enflurane administered, so as to maximize the difference between the awake and sedated state. A pulse oximeter (Ohmeda Biox 3740) continuously measured arterial oxygen saturation via a finger probe. The study was approved by the Central Oxford Research Ethics Committee.

During the experiment subjects were seated in a comfortable chair and breathed via a mouthpiece from an automated gas mixing system designed to regulate end-tidal values, which provided a steady stream of gas of 66 litre $\text{min}^{-1}$. Respiratory volumes were measured with a turbine volume measuring device.[20] Respiratory flows and timing information were obtained using a pneumotachograph. Respired gas was sampled at the mouth and analysed for $P\text{CO}_2$, $P\text{O}_2$ and enflurane by a mass spectrometer (Airspec 3000, Airspec Ltd., Biggin Hill, Kent, UK). All variables were recorded in real time with a 50-Hz sampling speed by an IBM PC computer. This computer executed a peak-picking program in real time to determine inspiratory and expiratory volumes and durations, and end-tidal $P\text{CO}_2$ ($P\text{E}'_{\text{CO}_2}$) and $P\text{O}_2$ ($P\text{E}'_{\text{O}_2}$). Breath-by-breath end-tidal values were passed to a second computer controlling the gas mixing system. This computer compared actual $P\text{E}'_{\text{CO}_2}$ and $P\text{E}'_{\text{O}_2}$ with the desired values, and adjusted the inspiratory gas mixture to maintain the desired end-tidal values independently of changes in ventilation. Details of the dynamic end-tidal forcing technique and gas mixing system have been described in more detail elsewhere.[21 22]

Enflurane was administered using a vaporizer (Penlon Ltd, Abingdon, UK) through which an air flow of 6–10 litre $\text{min}^{-1}$ was used. The mass spectrometer was calibrated using a standard gas mixture of 0.419% enflurane in air (British Oxygen Company, London; enflurane concentration certified to be within the range 0.398–0.440%). The mass number used for enflurane was 51. During experiments in which enflurane was administered the end-expired enflurane concentration was held constant at 0.34% by manual adjustment of the inspired concentration. During experiments in which no enflurane was administered the vaporizer was kept in the off position.

### EXPERIMENTAL DESIGN

Each subject was studied twice, on separate days. On each day four different tests were studied: (1) 0.2 MAC of enflurane with hypoxia, (2) 0.2 MAC of enflurane with euoxia, (3) no enflurane with hypoxia and (4) no enflurane with euoxia. In tests involving a period of hypoxia (hypoxia tests), $P\text{E}'_{\text{O}_2}$ was forced as follows: 8 min at 13.3 kPa, 20 min at 6.7 kPa and 8 min at 13.3 kPa. In tests involving no period of hypoxia (euoxia tests), $P\text{E}'_{\text{O}_2}$ was held constant at 13.3 kPa for 36 min. In both tests $P\text{E}'_{\text{CO}_2}$ was increased 0.67 kPa above the subject's natural value and maintained constant. The order of the tests was randomized and the tests were separated by 30–45-min intervals.

### DATA ANALYSIS

Data from each test were averaged over 60-s intervals. To characterize the change in the fast components of the ventilatory response to sustained hypoxia we used four particular 1-min periods, which are illustrated in figure 1. The four periods were: ventilation during the last minute before the step into hypoxia ($\dot{V}\text{E}_1$, pre-hypoxic or baseline ventilation), peak ventilation during the first 5 min of the hypoxic period ($\dot{V}\text{E}_2$, peak ventilation), ventilation during the last min of hypoxia ($\dot{V}\text{E}_3$, depressed ventilation) and minimum ventilation during the first 5 min after return to euoxia ($\dot{V}\text{E}_4$, post-hypoxic ventilation). The acute hypoxic ventilatory response (on-response, AHVR) was then taken as the

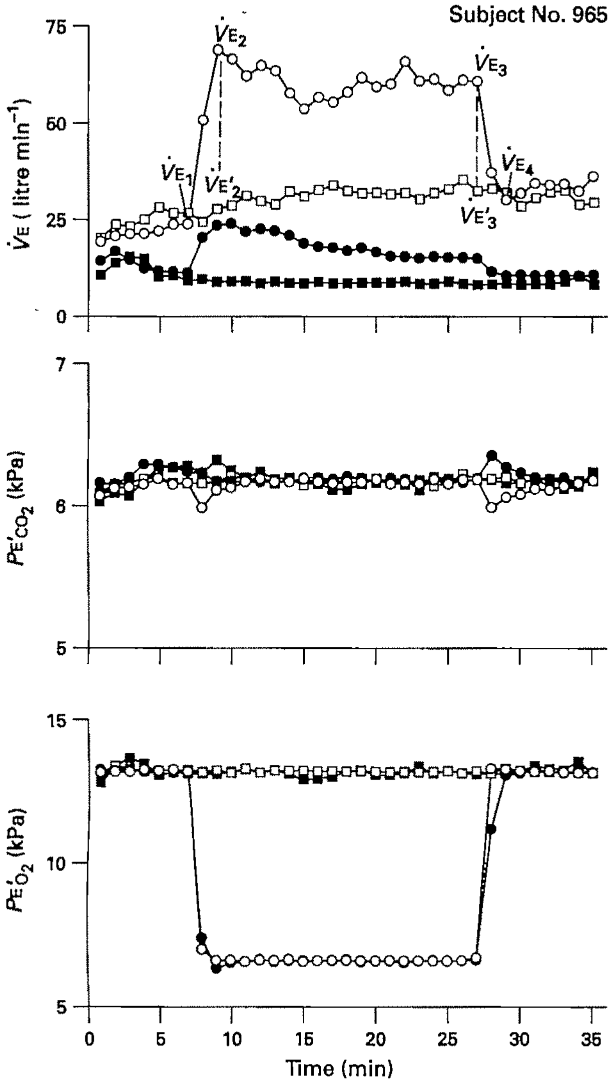

*Figure 1* Subject No. 965. Minute averages. Ventilation ($\dot{V}$E), end-tidal carbon dioxide partial pressure ($P$E$'_{CO_2}$) and end-tidal oxygen partial pressure ($P$E$'_{O_2}$) during hypoxia (circles) and euoxia (squares) tests. Open symbols represent studies without enflurane (○, □) and closed symbols (●, ■) studies with enflurane. Data shown are typical of those for all subjects. $\dot{V}$E$_1$, $\dot{V}$E$_2$, $\dot{V}$E$_3$, $\dot{V}$E$_4$, $\dot{V}$E$'_2$ and $\dot{V}$E$'_3$ indicate ventilations referred to in the text.

difference between peak ventilation and pre-hypoxic ventilation ($\dot{V}$E$_2-\dot{V}$E$_1$). The magnitude of the off-response was calculated as the difference in ventilation between the depressed ventilation and post-hypoxic ventilation ($\dot{V}$E$_3-\dot{V}$E$_4$). The decline in ventilation during hypoxia was corrected for changes in ventilation during the euoxia tests. Thus HVD was calculated using the values of ventilation ($\dot{V}$E$'_2$ and $\dot{V}$E$'_3$) measured during euoxia tests corresponding in time to peak and depressed ventilation (fig. 1). We used the formula: HVD$=(\dot{V}$E$'_2-\dot{V}$E$'_3)-(\dot{V}$E$'_2-\dot{V}$E$'_3)$.

The significance of differences in baseline ventilation, AHVR, HVD and off-response between the two pharmacological conditions was assessed by analysis of variance (ANOVA; balanced design). The analysis was run within MS Windows for Workgroups 3.11 on a Dell XPS P120c PC, using the Minitab for Windows software package. A probability level of less than 0.05 was taken as statistically significant.

## Results

Three of the initial 13 subjects recruited for the study failed to complete the experiments; one because of the excitation, nausea and discomfort during enflurane inhalation and the other two because they found they could not afford the time. The remaining 10 subjects completed the study without any adverse effect. During the enflurane experiments the level of sedation was intense. All of our subjects performed the enflurane experiments with closed eyes. In four subjects we observed airway obstruction with enflurane; this was relieved in all cases by gentle manual extension of the head, traction on the mandible, or both. One subject included in the study had some mild excitation. Mean values for inspired and end-tidal anaesthetic concentrations are shown in table 1. MAC for enflurane was taken to be 1.7%.[23]

End-tidal gas profiles for each test and each pharmacological condition are given in table 2. Figure 2 demonstrates the quality of the end-tidal gas control and ventilatory responses of one subject (No. 960) for the hypoxia and euoxia tests for both pharmacological conditions, each repeated twice. In the hypoxia test the steps of $P$E$'_{O_2}$ into and out of hypoxia were rapid (fig. 2, left bottom panel; for means see fig. 3C). In the euoxia test, $P$E$'_{O_2}$ was maintained constant (fig. 2, right bottom panel; for means see fig. 3C). In both tests $P$E$'_{CO_2}$ remained constant with the exception of a small increase immediately after the step out of hypoxia in the presence of enflurane (fig. 2, middle panels; for means see fig. 3B).

Figure 3 illustrates mean ventilations for all 10 subjects in the euoxia and hypoxia tests under two pharmacological conditions. All subjects showed biphasic ventilatory responses to sustained hypoxia

*Table 1* Mean (SEM) values for inspired (%) and end-tidal (% and MAC) concentrations of enflurane during the two tests (hypoxia, euoxia)

| Target | | Actual | |
|---|---|---|---|
| End-tidal (%) | Inspired (%) | End-tidal (%) | End-tidal (MAC) |
| Hypoxia test | | | |
| 0 | 0 | 0.007 (0.002) | 0.006 (0.002) |
| 0.34 | 0.484 (0.013) | 0.342 (0.004) | 0.201 (0.002) |
| Euoxia test | | | |
| 0 | 0 | 0.012 (0.002) | 0.007 (0.001) |
| 0.34 | 0.497 (0.011) | 0.352 (0.002) | 0.207 (0.001) |

*Table 2* Mean (SEM) end-tidal $P$CO$_2$ and end-tidal $P$O$_2$ partial pressures for hypoxia and euoxia tests, each with and without enflurane

| | Hypoxia | | | | Euoxia | |
|---|---|---|---|---|---|---|
| | | $P$E$'_{O_2}$ (kPa) | | | | |
| | $P$E$'_{CO_2}$ (kPa) | Pre-hyp. | Hyp. | Post-hyp | $P$E$'_{CO_2}$ (kPa) | $P$E$'_{CO_2}$ (kPa) |
| No enflurane | 5.91<br>(0.08) | 13.29<br>(0.01) | 6.73<br>(0.01) | 13.35<br>(0 01) | 5.94<br>(0.08) | 13 30<br>(0.0) |
| Enflurane | 5.99<br>(0.07) | 13.23<br>(0.01) | 6.70<br>(0.01) | 13.10<br>(0.04) | 5.96<br>(0.08) | 13.29<br>(0.01) |

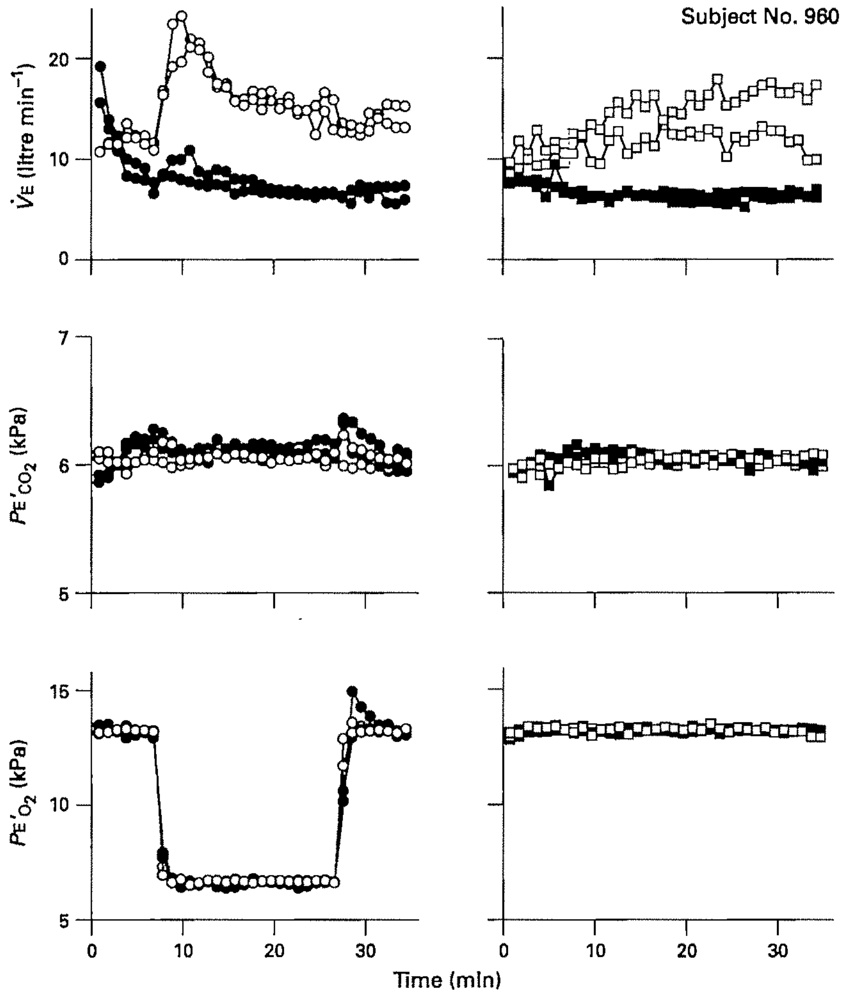

*Figure 2* Subject No. 960, individual responses. Minute averages. Ventilation ($\dot{V}_E$), end-tidal carbon dioxide partial pressure ($P_{E'CO_2}$) and end-tidal oxygen partial pressure ($P_{E'O_2}$) during hypoxia (left) and euoxia (right) tests. Open symbols represent studies without enflurane and closed symbols studies with enflurane.

*Table 3* Ventilatory response characteristics (litre min$^{-1}$) to sustained hypoxia for all subjects during control and enflurane conditions

| Subject No. | Control | | | | Enflurane | | | |
|---|---|---|---|---|---|---|---|---|
| | $\dot{V}_{E_1}$ | AHVR | HVD | Off | $\dot{V}_{E_1}$ | AHVR | HVD | Off |
| 928 | 20.0 | 28.2 | −0.2 | 28.4 | 5.0 | 2.3 | 0.6 | 1.4 |
| | 19.0 | 35.0 | 11.1 | 16.2 | 5.0 | 2.5 | 2.3 | 1.1 |
| 956 | 15.4 | 11.4 | 6.7 | 5.1 | 13.3 | 2.0 | 5.1 | 0.5 |
| | 15.7 | 10.6 | 0.8 | 6.8 | 13.1 | 12.5 | 5.9 | 3.6 |
| 960 | 10.7 | 12.6 | 7.0 | 2.5 | 7.5 | 0.3 | 0.6 | 0.3 |
| | 11.4 | 7.6 | 10.4 | 0.2 | 6.4 | 3.4 | 3.7 | 0.4 |
| 965 | 23.4 | 45.3 | 16.0 | 30.9 | 10.7 | 12.9 | 8.5 | 3.5 |
| | 35.3 | 65.5 | 46.2 | 31.1 | 10.8 | 7.5 | 9.2 | 2.6 |
| 966 | 19.6 | 9.2 | 2.0 | 4.0 | 20.3 | 18.1 | 9.0 | 9.1 |
| | 18.5 | 11.1 | 3.4 | 10.5 | 16.5 | 0 | 6.5 | 3.9 |
| 971 | 16.2 | 12.2 | 2.2 | 6.0 | 8.6 | 0.7 | −0.2 | 0.2 |
| | 17.3 | 11.5 | −5.0 | 9.8 | 9.5 | 0.1 | 1.6 | 1.9 |
| 972 | 30.5 | 31.7 | 15.8 | 21.5 | 17.0 | 11.8 | 21.0 | 1.2 |
| | 46.0 | 29.4 | 0.6 | 31.7 | 13.2 | 13.7 | 13.5 | 1.4 |
| 973 | 15.9 | 17.5 | 6.9 | 7.8 | 10.1 | −3.2 | 1.6 | 1.4 |
| | 31.6 | 12.4 | 10.1 | 5.4 | 6.9 | 1.7 | 6.1 | 0.1 |
| 974 | 15 5 | 13.7 | 12.6 | 5.0 | 6.8 | 2.3 | 3.1 | 0.8 |
| | 16.0 | 8.9 | 13.6 | 4.5 | 7.4 | 2.8 | 4.8 | 0.3 |
| 981 | 17.5 | 11.6 | 11.5 | 1.9 | 5.5 | 6.2 | 4.3 | 1.2 |
| | 22.6 | 15.5 | 5.3 | 4.9 | 7.6 | 1.8 | 1.7 | 0.8 |
| Mean | 20.9 | 20.1 | 8.9 | 11 7 | 10.1 | 5.0 | 5.5 | 1.8 |
| SEM | 2.0 | 3.3 | 2.4 | 2.4 | 1.0 | 1.3 | 1.1 | 0.5 |

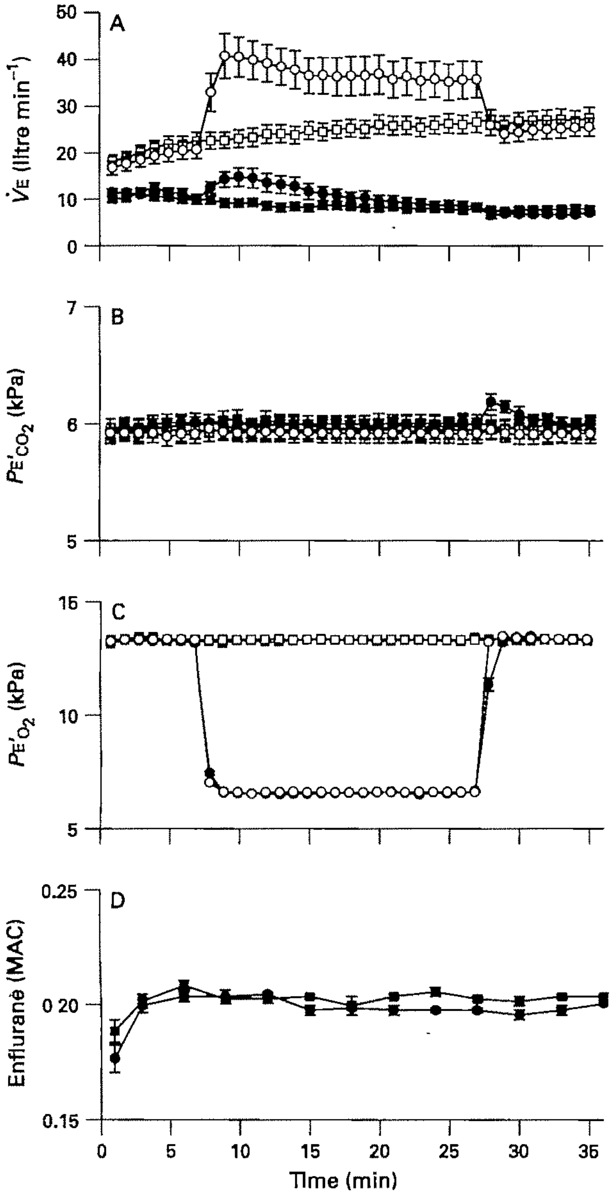

*Figure 3* Mean values for all 12 subjects for ventilation ($\dot{V}$E) (A), end-tidal carbon dioxide partial pressure ($P$E'$_{\text{CO}_2}$) (B) and end-tidal oxygen partial pressure ($P$E'$_{\text{O}_2}$) (C). ○=Hypoxia tests without enflurane; ●=hypoxia tests with enflurane; □=euoxia tests without enflurane; ■=euoxia tests with enflurane. Also shown is the end-tidal enflurane concentration in euoxia (■) and hypoxia (●) (D).

when no enflurane was administered. The biphasic responses to hypoxia were sometimes less obvious during enflurane sedation. The ventilatory responses to hypoxia were generally greater in the absence of enflurane than during enflurane sedation. In the absence of enflurane in the euoxia test ventilation increased gradually over the whole experimental period (fig. 3A), whereas in the presence of enflurane in the euoxia test, ventilation decreased gradually over most of the time (fig. 3A). In the presence of enflurane, the increase in $P$E'$_{\text{CO}_2}$ failed to increase ventilation substantially as was planned (fig. 3A).

Individual values for baseline ventilation, AHVR, HVD and off-responses together with their means are shown in table 3. There was a significant reduction in baseline ventilation ($F$=21.71, $P$<0.001), AHVR ($F$=13.04, $P$<0.01) and off-response ($F$=8.86, $P$<0.02) when comparing enflurane administration with control. In contrast with these findings for baseline ventilation, AHVR and the off-response, there was no significant difference in the magnitude of HVD between the two pharmacological conditions ($F$=1.697, ns).

As an alternative to comparing absolute values for AHVR, HVD and off-response with and without enflurane, it is also possible to compare AHVR, HVD and off-responses with and without enflurane when they are expressed as ratios of baseline ventilation ($\dot{V}$E$_1$) before hypoxia is imposed. Under these conditions AHVR/$\dot{V}$E$_1$ and off-response/$\dot{V}$E$_1$ were both reduced significantly by enflurane ($F$=12.85, $P$<0.01; $F$=12.12, $P$<0.01, respectively), demonstrating that the effect of enflurane was greater on AHVR and off-response than on baseline ventilation. In contrast with the significant findings for AHVR/$\dot{V}$E$_1$ and off-response/$\dot{V}$E$_1$, there was no significant effect for HVD/$\dot{V}$E$_1$ ($F$=0.45, ns). This suggests that our study could not distinguish between the magnitude of HVD remaining constant with and without enflurane and the magnitude of HVD diminishing in proportion to baseline ventilation.

In order to determine if our study could distinguish between HVD remaining constant and HVD changing in proportion to AHVR, we compared the effect of enflurane on HVD/AHVR. A parametric test of significance was inappropriate in this case because of a number of small values of AHVR giving rise to very large values for HVD/AHVR. To overcome this, a non-parametric test (Friedman test) was used, which demonstrated a significant increase in HVD/AHVR with enflurane ($S$=6.40, $P$<0.02).

In order to see if peripheral chemoreflex sensitivity to hypoxia remained unchanged during sustained hypoxia, we compared the magnitude of AHVR and off-response in both pharmacological conditions. The off-response was significantly smaller than AHVR in both cases ($t$ test, $P$<0.001 without enflurane, $P$<0.01 with enflurane). However, the ratio of off-response to AHVR did not differ significantly with and without enflurane ($F$=0.54, ns), suggesting that the proportionate decline in the ventilatory sensitivity to hypoxia was unchanged by enflurane.

## Discussion

The experiments were performed against a background of mild hypercapnia in order to increase the level of ventilation before induction of hypoxia. The idea behind this was that the magnitude of the rapid decrease in ventilation after relief of hypoxia would then not be limited by the need to maintain some basal level of ventilation,[19] that is ventilation would then be able to decrease well below the pre-hypoxic level but still be above the normal eucapnic level. In this respect our study was unsuccessful, as the level of sedation was sufficiently intense effectively to bring ventilation back to basal levels despite the increase in end-tidal $P$CO$_2$. Consequently, conclusions relating to the magnitude of the off-transient during enflurane sedation from this study should be drawn with care (see below).

In addition to performing the hypoxia experiments, we also performed the experiments without hypoxia because we were aware of the possibility that ventilation under the condition of moderate hypercapnia might change gradually with time.[19 24 25] These experiments enabled us to control for any gradual change in hypercapnia over time when interpreting the response to sustained hypoxia. We found that under moderate hypercapnic conditions, euoxic ventilation increased gradually over the whole experimental period in subjects exposed to no enflurane, and decreased gradually in subjects exposed to enflurane. This finding was unexpected, and raises the possibility that the effects of constant end-tidal enflurane were not steady throughout the exposure, but rather that the level of sedation increased progressively.

### ACUTE HYPOXIC VENTILATORY RESPONSE (AHVR): EFFECT OF LOW-DOSE ENFLURANE

The observation that a sub-anaesthetic concentration of enflurane (0.2 MAC) markedly depressed the ventilatory response to acute hypoxia was no surprise.[2 3] Knill, Manninen and Clement reported a 55% reduction in AHVR at 0.1 MAC of enflurane.[2] We found a significant reduction in AHVR of 75%. In our previous study we observed that AHVR was reduced by 20%, 44% and 55% at 0.05, 0.1 and 0.2 MAC of enflurane, respectively.[3] This indicated a steep dose-response curve for the effects of sub-anaesthetic concentrations of enflurane on hypoxic drive. The somewhat greater reduction in AHVR found in this study for 0.2 MAC of enflurane compared with our previous study may be because of different levels of stimulation of our subjects in the two studies. In the previous study[3] subjects were asked to watch television and remain attentive, whereas in this study subjects were asked to close their eyes and the room was partially darkened and kept quiet.

### HYPOXIC VENTILATORY DECLINE (HVD)

We were unable to detect a significant effect of 0.2 MAC of enflurane on hypoxic ventilatory decline. This is consistent with earlier studies on halothane,[4 6] isoflurane[7-9] and enflurane[3] and supports the notion that AHVR and HVD can be targeted separately and may therefore arise via independent mechanisms. Thus in a functional sense, enflurane would appear to affect the ventilatory response to sustained hypoxia in a manner similar to that of dopamine,[26] producing a reduction in AHVR while HVD is unchanged.

We have noted, however, that our study did not have sufficient power to distinguish between the magnitude of HVD remaining constant with and without enflurane and the magnitude of HVD diminishing with enflurane in proportion to baseline ventilation. Our statistical analysis does, however, demonstrate as unlikely that HVD is reduced by enflurane in proportion to AHVR. This in turn suggests that enflurane does not have the effect of modifying the whole ventilatory profile ($\dot{V}_{E_1}$, AHVR, HVD) at all times by the same proportionate reduction.

It is important, however, to bear in mind one possible interpretation of our measurement of a relatively large HVD (5.5 litre min$^{-1}$, table 3) in the presence of enflurane, namely that there may have been a progressive intensification of the effect of enflurane on the peripheral chemoreflex during the hypoxia tests and this would have confounded our attempt to measure HVD in the presence of a constant level of anaesthesia. In effect the "acute" component of the ventilatory response to hypoxia may have been steadily declining through a progressive intensification of the effects of enflurane during the 20-min hypoxic exposure, rendering our measurement of HVD an overestimate. It is to be noted that, although the formula for calculating HVD allows for any progressive effects of enflurane on euoxic ventilation, it cannot allow for a progressive depression by enflurane of the peripheral chemoreflex. An experimental observation that supports this notion is that enflurane reversed the normal progressive increase in ventilation observed with hypercapnia during euoxia. The simplest interpretation of this finding is that the effects of enflurane are not steady, but becoming progressively more intense. However, we know of no evidence that the central neural effects of inhalation anaesthesia change progressively with time in the presence of a constant end-tidal pressure of the anaesthetic over the duration studied here.

### AHVR *VS* OFF-TRANSIENT: EFFECT OF LOW-DOSE ANAESTHETICS

Our observation that in the presence of enflurane the rapid decrease in ventilation at cessation of hypoxia was not similar in magnitude to AHVR seems at variance with the findings of Dahan and coworkers.[6] They studied the effects of 0.15 MAC of halothane on the ventilatory response to sustained mild hypercapnic hypoxia (end-tidal $P\text{CO}_2$ 0.13 kPa above subject's natural value). They observed a small ventilatory undershoot after relief of hypoxia in the absence of anaesthetic, but a larger undershoot in the presence of halothane. Their finding that there was no significant difference in the magnitude of AHVR and the off-response (AHVR=3.6 litre min$^{-1}$; off-response=3.9 litre min$^{-1}$) in the presence of halothane, suggested that the peripheral reflex sensitivity remained unchanged by sustained hypoxia under these conditions.

Our study was designed to provide sufficient elevation of pre-hypoxic ventilation to enable a symmetric off-transient to occur in the presence of enflurane without the limitation of hypopnoea or apnoea on the transition from hypoxia to euoxia. Under enflurane sedation, however, our technique of using moderate hypercapnia failed to achieve a substantial increase in ventilation above normal levels, and the design must therefore be regarded as having failed in this respect. The extent to which a persistent minimum ventilation linked to wakefulness (or "ventilatory dog-leg", as it is often known in the context of studies of hypercapnic sensitivity) is retained in humans under sedation remains uncertain, and with it the extent to which ventilation would need to be increased to permit a symmetrical off-response after a period of sustained hypoxia. It would be informative to repeat administration of enflurane in the presence of a substantially higher level of hypercapnia.

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LABORATORY INVESTIGATIONS

# Effect of exogenous nitric oxide and superoxide on interleukin-8 from human polymorphonuclear leucocytes

B. H. CUTHBERTSON, H. F. GALLEY AND N. R. WEBSTER

## Summary

Patients with acute inflammatory lung injury are commonly treated with inhaled nitric oxide. Nitric oxide has profound immunoregulatory effects. Increased concentrations of the cytokine interleukin-8 (IL-8) in bronchoalveolar lavage fluid has been associated with disease severity. We have investigated the effects of a nitric oxide donor and a combined nitric oxide–superoxide donor on lipopolysaccharide-mediated accumulation of IL-8 from cultured human neutrophils. Interleukin-8 was measured in culture supernatant after 20 h using enzyme immunoassay. The combined nitric oxide–superoxide donor, 3-morpholinosydnonimine (SIN-1), dose-dependently decreased lipopolysaccharide-mediated IL-8 accumulation ($P<0.01$). SIN-1 also decreased IL-8 accumulation from unstimulated neutrophils ($P<0.001$). In contrast, the pure nitric oxide donor, 1,2,3,4-oxatriazolium 5-amino chloride (GEA-3162), increased stimulated IL-8 accumulation ($P<0.01$) and also increased IL-8 accumulation in unstimulated cells ($P<0.002$). Nitric oxide and superoxide have profound effects on IL-8. These results have important implications for the treatment of patients with acute lung injury with inhaled nitric oxide. (*Br. J. Anaesth.* 1997; **78**: 714–717).

**Key words**
Polypeptides, cytokines. Pharmacology, nitric oxide. Lung, damage. Lung, adult respiratory distress syndrome.

Nitric oxide has been found to have many biological roles within the body and nitric oxide gas is used as a selective pulmonary vasodilator in critically ill patients with acute respiratory distress syndrome (ARDS).[1] A variety of mediators have been shown to reflect the severity of lung inflammation in ARDS. Concentrations of the cytokine interleukin-8 (IL-8) in bronchoalveolar lavage fluid correlated with the development of ARDS[2] and increased IL-8 concentrations early in the disease process correlated with mortality.[3] In addition, inhaled nitric oxide therapy modulates increased cytokine concentrations, including IL-8, in patients with ARDS.[4]

Nitric oxide and its metabolite peroxynitrite are known to have a profound effect on the inflammatory process as it is now known that activated white cells release nitric oxide in addition to superoxide anion during the respiratory burst.[5] There is however, little information on the possible interaction of nitric oxide and the metabolites of nitric oxide on the regulation of the inflammatory process. Such regulation is governed by circulating inflammatory mediators which are released from immune cells and affect the functioning of other cells. Information on this interaction is important because of the increasing use of exogenous nitric oxide in the treatment of refractory hypoxia and pulmonary hypertension in ARDS.

We have therefore investigated the effects of nitric oxide and superoxide on cytokine production by polymorphonuclear leucocytes both with and without lipopolysaccharide and in the presence of either the nitric oxide donor 1,2,3,4-oxatriazolium 5-amino chloride (GEA-3162) or the combined nitric oxide and superoxide donor 3-morpholinosydnonimine (SIN-1).

## Materials and methods

Polymorphonuclear leucocytes were isolated from a single volunteer for all experiments using a single step density gradient procedure. Arterial blood was added to sterile preservative-free heparin (10 u./ml of blood) and layered onto Polymorphprep separation medium (Nycomed UK Ltd, Birmingham, West Midlands, UK). After centrifugation at 475 *g* for 35 min at 20 °C, the mononuclear cell band was discarded and polymorphonuclear leucocytes (PMN) were retrieved and washed in Dulbecco's modification of Eagle's basal medium (DMEM, ICN Biomedicals Ltd, Thame, Oxon, UK). Contaminating erythrocytes were removed by hypotonic shock and cells were washed three times in DMEM before being resuspended, counted and adjusted to $3\times10^6$ cells/ml.

Replicate samples ($1.5\times10^6$ cells) were placed into 24-well tissue culture plates and lipopolysaccharide to a final concentration of 1.7 $\mu$g ml$^{-1}$ (LPS, from *E. coli* strain 0111.B4, Sigma-Aldrich Chemical Co. Ltd, Poole, Dorset, UK) or phosphate-buffered

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saline blank was added as appropriate. To each well was also added varying concentrations of the nitric oxide donors. The agents used were 3-morpholinosydnonimine hydrochloride (SIN-1) (Alexis Corporation, Nottingham, UK) which is a metabolite of the vasodilator molsidomine and is a nitric oxide and superoxide anion donor and thus considered a peroxynitrite releasing compound. In addition, to some cells was added 1,2,3,4-oxatriazolium-5-amino-3-(3,4-dichlorophenyl)-chloride (GEA-3162) (Alexis Corporation, Nottingham, UK) which is a water soluble nitric oxide donor. The concentrations used were 10, 100 and 1000 μmol litre$^{-1}$ for SIN-1 and 0.01, 0.1 and 1.0 μmol litre$^{-1}$ for GEA-3162 in phosphate-buffered saline. Non-LPS stimulated neutrophils were also incubated with SIN-1 100 μmol litre$^{-1}$ or GEA-3162 1 μmol litre$^{-1}$ as controls.

Tissue culture plates were incubated at 37 °C in an atmosphere of 5% carbon dioxide–95% air for 20 h. Culture medium was removed for measurement of IL-8 using solid phase sandwich enzyme-linked immunosorbent assay (ELISA, R&D Systems Europe Ltd, Abingdon, Oxon, UK). Results are expressed as pg/10$^6$ cells. The assay is highly specific for IL-8 and shows no cross-reactivity for any of the other human cytokines tested. Within-assay precision was 3.2% ($n$=20) and between-assay precision 9.5% ($n$=20). Cells were detached for viability count using the vital stain trypan blue.

### STATISTICAL ANALYSIS

Data are presented as median (range) and represent 5–6 separate experiments. Statistical analysis was performed using Microsoft Excel with Astute add-in and data were analysed using Kruskal–Wallis analysis of variance or Mann–Whitney $U$ test as appropriate, with $P<0.05$ being considered statistically significant.

## Results

Unstimulated polymorphonuclear leucocytes produced detectable basal concentrations of IL-8 which were increased when cells were incubated with LPS ($P<0.0001$; figs 1, 2). Incubation with SIN-1 caused concentration-dependent depression of IL-8 accumulation in culture medium of LPS-stimulated cells ($P<0.01$; fig. 1). Addition of SIN-1 1000 μmol litre$^{-1}$ to cells in the absence of stimulation with LPS also caused a reduction in basal IL-8 accumulation ($P<0.001$; fig. 1).

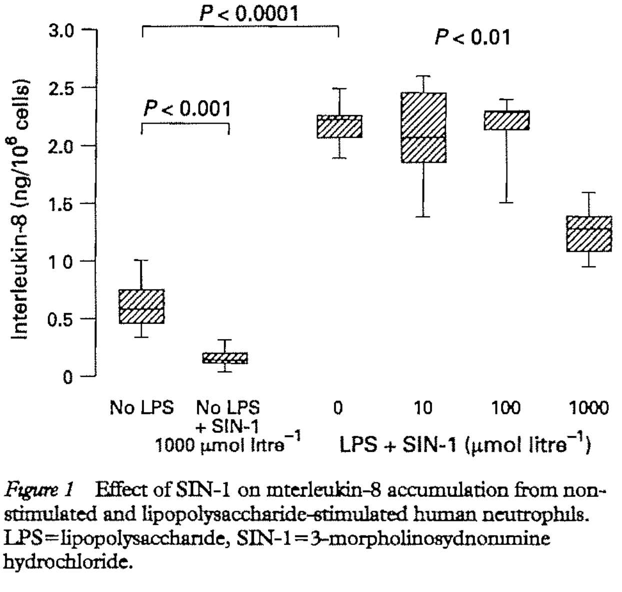

*Figure 1* Effect of SIN-1 on interleukin-8 accumulation from non-stimulated and lipopolysaccharide-stimulated human neutrophils. LPS=lipopolysaccharide, SIN-1=3-morpholinosydnonimine hydrochloride.

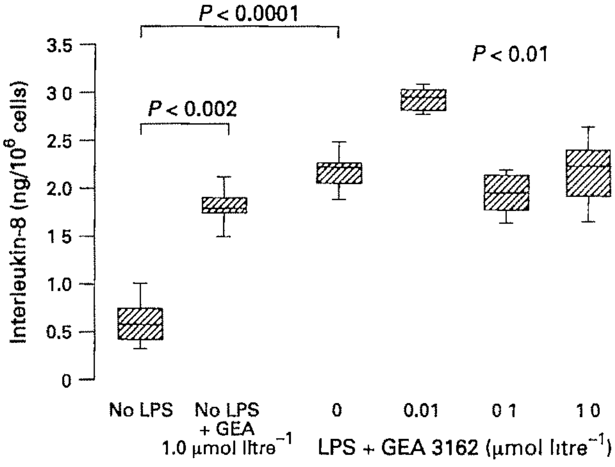

*Figure 2* Effect of GEA-3162 on interleukin-8 accumulation from non-stimulated and lipopolysaccharide-stimulated human neutrophils. LPS=lipopolysaccharide, GEA-3162=1,2,3,4-oxatriazolium-5-amino-3-(3,4-dichlorophenyl)-chloride.

In contrast, GEA significantly increased IL-8 accumulation from both LPS-stimulated and unstimulated cells ($P<0.01$ and $P<0.002$ respectively; fig. 2).

Trypan blue staining showed that cell viability in SIN-1 and GEA-3162 treated cells after 20 h incubation was similar to that of cells in the absence of these agents.

## Discussion

We have shown that exogenous nitric oxide and a combination of nitric oxide–superoxide has a marked effect on the accumulation of IL-8 from LPS-stimulated human polymorphonuclear leucocytes. IL-8 is a potent neutrophil chemotactic and activating factor released by neutrophils in a self-amplifying process in response to inflammatory stimuli. IL-8 has been implicated in the pathogenesis of ARDS both as a marker of onset and severity of ARDS,[2] and concentrations in bronchoalveolar lavage fluid correlate with mortality.[3] It is a potent chemoattractant and has an important role in the recruitment and activation of neutrophils into the lung. Activated neutrophils via the release of cytokines, proteinases, hypochlorous acid, oxygen-derived free radicals and nitric oxide are important in the pathophysiology of ARDS as these inflammatory mediators may result in tissue damage. Further release of these chemotactic factors potentiates this inflammatory process. Factors which regulate the production and release of IL-8 may, therefore, have a major role in altering the regulation of inflammation. The release of IL-8 by the same cell type as that on which it acts has important implications as it so acts to amplify the inflammatory process occurring at that particular site. For these reasons the study of isolated neutrophils *in vitro* provides a model of the pathophysiological processes in ARDS. The dedicated nitric oxide donor GEA and the combined nitric oxide–superoxide anion donor SIN-1 had markedly different effects on IL-8. Such changes have clear implications for patients receiving inhaled nitric oxide for the acute inflammatory process of ARDS.

Exogenous nitric oxide has been shown to have various effects on the activity of neutrophils. Production of the arachidonic acid product leukotriene $B_4$ is dose-dependently reduced in the presence of either SIN-1 or GEA-3162 in calcium ionophore-stimulated neutrophils.[6] In addition, there is a dose-dependent reduction in leukotriene $B_4$ formation in formyl-methionyl-leucyl-phenylalanine- (FMLP) stimulated neutrophils in the presence of SIN-1.[7] There is some evidence of a biphasic effect of SIN-1 on the oxidative burst activity (superoxide production) of opsonised zymosan-activated neutrophils.[8] Other investigators have shown dose-dependent reduction in superoxide production by SIN-1 in stimulated and non-stimulated neutrophils.[9] Nitric oxide can inhibit the enzyme NADPH oxidase which produces superoxide.[10] Nitric oxide has also been shown to reduce neutrophil adherence and migration and thus accumulation.[11]

We have found a different effect of dedicated nitric oxide donor compared with the combined nitric oxide–superoxide anion donors on human polymorphonuclear leucocytes. Exogenous nitric oxide alone increased the accumulation of IL-8 in both LPS-stimulated and unstimulated neutrophils. The combined nitric oxide–superoxide anion donor (effectively a peroxynitrite donor) caused a concentration-dependent reduction in IL-8 production. This is in contrast with a previous study of human melanoma cells in which both SIN-1 and the dedicated nitric oxide donors S-nitroso-L-glutathione and S-nitroso-N-acetylpenacillamine caused an increase in IL-8 at the transcriptional level.[12] Another study using a human endothelial cell line showed that exogenous nitric oxide increased IL-8 release.[13] These effects may represent different actions on the transcription factor nuclear factor κB (NFκB) in the cell types described. This transcription factor is activated by external cell signals and allows rapid production of immunologically active compounds such as cytokines and nitric oxide synthase. It is known that activation of NFκB is stimulated by hydrogen peroxide and possibly other free radicals[14] and that nitric oxide also activates NFκB in some cell types,[12 15] although in human endothelial cells NFκB is inhibited by nitric oxide.[16] The effect of nitric oxide and superoxide on NFκB activation or inhibition in human neutrophils is not known. It is also possible that nitric oxide and superoxide could affect transcriptional, translational, post-translational and stability or excretion of IL-8 after its production. Further research to elucidate the role of free radicals on inflammatory responses is required

The relative levels of nitric oxide and peroxynitrite could determine the recruitment of neutrophils into the lung either through a direct effect of nitric oxide on neutrophil adherence or through IL-8 induced chemotaxis. During inhaled nitric oxide therapy in ARDS this balance may be disturbed thereby resulting in alteration of the inflammatory process. Inhaled nitric oxide therapy has been shown to decrease the high IL-6 and IL-8 concentrations in bronchoalveolar lavage fluid in patients with ARDS.[4] These results contradict our findings but could be explained by the high availability of superoxide in inflammatory lung diseases leading to peroxynitrite production.[17] This would agree with work that showed the presence of nitrotyrosin residues (a marker of peroxynitrite damage) within the lung of all patients with ARDS and would explain decreased IL-8 concentrations in bronchoalveolar lavage fluid in these patients.[4 18]

The precise role of exogenously administered nitric oxide in the regulation of the inflammatory process still needs to be established in the intact human.

## Acknowledgements

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# Effects of volatile anaesthetics on human neutrophil oxidative response to the bacterial peptide FMLP

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## Summary

The oxidative burst response of neutrophils to bacteria is crucial for effective host defence. It has been shown that inhalation anaesthetics interfere with neutrophil function and the object of this study was to characterize the mechanisms of interaction of volatile anaesthetics with the oxidative response of neutrophils. $H_2O_2$ production by neutrophils after stimulation with the bacterial peptide, *N*-formyl-L-methionyl-L-leucyl-phenylalanine (FMLP) and phorbol-12-myristate-13-acetate (PMA) was measured by oxidation of the indicator dye dihydrorhodamine using flow cytometry. FMLP binds to a specific surface receptor on neutrophils and initiates via receptor specific signal transduction respiratory burst as an all-or-none event, whereas PMA is an artificial activator of protein kinase C, which bypasses receptor-mediated signal transduction. In the presence of halothane, enflurane and sevoflurane, there was an increase in activation threshold on FMLP stimulation. Overall, this correlated with reduced $H_2O_2$ production. Isoflurane had no effect. In the presence of desflurane, however, $H_2O_2$ production of neutrophils increased two-fold, followed by transient suppression of neutrophil function. PMA-induced $H_2O_2$ generation was unchanged in the presence of volatile anaesthetics. We conclude that volatile anaesthetics modulated FMLP receptor-dependent signal transduction upstream of protein kinase C activation, leading to a reduced response in the presence of halothane, enflurane and sevoflurane and to an increased response in the presence of desflurane. (*Br. J. Anaesth.* 1997; **78**: 718–723).

**Key words**
Immune response. Blood, leucocytes Blood, neutrophils. Anaesthetics volatile, desflurane. Anaesthetics volatile, enflurane. Anaesthetics volatile, halothane. Anaesthetics volatile, isoflurane Anaesthetics volatile, sevoflurane.

Neutrophil granulocytes are a major component of the non-antigen-specific, cell-mediated immune system. Activated by chemotactic signals, neutrophils migrate towards infected tissue ingesting and killing bacteria. A crucial mechanism of bacterial killing by neutrophils is generation of reactive oxygen derivatives. Because of the high oxygen uptake during generation of reactive oxygen species, this reaction has also been called respiratory burst.[1]

The defence mechanism of oxygen radical production may be impaired, for example after drug exposure or during disease. Numerous studies have shown suppression of neutrophil oxidative function with halothane[2–6] and enflurane.[5–7] Isoflurane appears to have no, or only a minimal effect on neutrophils.[3–5 7]

We have investigated the effects of several halogenated, volatile anaesthetics on the production of reactive oxygen derivatives in human neutrophils. Two different stimuli, *N*-formyl-methionyl-leucyl-phenylalanine and phorbol-13-myristate-12-acetate, were used to trigger respiratory burst in order to discriminate between receptor-dependent and independent mechanisms, respectively.

The flow cytometric assay used in this study allows quantification of the heterogenous oxidative response of neutrophils at the single cell level with low degrees of stimulation.

## Materials and methods

The volatile anaesthetics used were obtained from the following companies: halothane from Hoechst, Germany; enflurane, sevoflurane and isoflurane from Abbott, Germany; desflurane from Pharmacia, Sweden. Carboxy-seminaphthorhodafluor-1-acetoxymethylester (SNARF1/AM) and dihydrorhodamine-123 (DHR) were obtained from Molecular Probes, Eugene, OR, USA. Dulbecco's phosphate-buffered saline (PBS) with $Ca^{2+}$ and $Mg^{2+}$ was obtained from Gibco-Life Technologies, Germany. *N*-formyl-L-methionyl-L-leucyl-phenylalanine (FMLP) and phorbol-12-myristate-13-acetate (PMA) were obtained from Sigma Chemicals,

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Deisenhofen, Germany. Propidium iodide (PI) was purchased from Serva, Heidelberg, Germany. DHR, SNARF1/AM and FMLP were kept as stock solutions in dimethylformamide (DMF) and diluted in PBS yielding working concentrations of 100 $\mu$mol litre$^{-1}$ for DHR, and 10 $\mu$mol litre$^{-1}$ for SNARF1/AM, FMLP and PMA. Stock solutions were stored at −70 °C. Standard dye-beads (Quantum 26) for calibration of the flow cytometer were obtained from Flow Cytometry Standards Europe based in Leiden, The Netherlands.

### ISOLATION OF LEUCOCYTES

This study was approved by the local Ethics Committee, and after receiving written informed consent, venous blood was obtained from healthy donors with no history of infection for the 2 weeks before the experiments. The donors ($n$=9) had a mean age of 32 (range 25–39) yr. They had a mean white blood cell count of 6200 (SD 1300)/$\mu$l and haemoglobin concentration was 15.2 (1.8) g dl$^{-1}$. Mean differential leucocyte count was: neutrophils 53 (8) %, lymphocytes 32 (7) %, monocytes 8 (3) %, eosinophils 3 (2) % and basophils 1 (1) %. Blood counts were performed before each experiment with a Technicon H*3 counter (Bayer Diagnostics, Tarrytown, NY, USA). No specimens had to be excluded because of abnormal blood cell counts.

Blood was collected in lithium heparin coated disposable blood sampling tubes (Sarstedt, Nürmbrecht, Germany). Leucocyte isolation was carried out by sedimenting erythrocytes on Ficoll. Heparinized (10 u. ml$^{-1}$) whole blood (3 ml) was layered on top of 3 ml of lymphocyte separation medium (density 1.077 g ml$^{-1}$) from Sigma Chemicals, Deisenhofen, Germany. Erythrocytes aggregated at the interface and settled at room temperature without centrifugation. After 40 min the upper 800 $\mu$l of supernatant leucocyte-rich plasma were withdrawn, avoiding contact with the plasma fraction close to the interface with the separation medium. To avoid artificial activation of cells, the isolation process did not involve lysis, centrifugation or washing procedures.

### RESPIRATORY BURST ASSAY

Each volatile anaesthetic was tested separately *in vitro* with neutrophils from the nine donors at four different concentrations (0, 0.5, 1.0, 2.0 MAC). The MAC values used for this study were: 0.8% for halothane, 1.7% for enflurane, 2% for sevoflurane, 1.2% for isoflurane and 6% for desflurane.[8 9] All anaesthetics were administered as volatile anaesthetic/air mixtures. The respiratory burst assay was performed in a 75 L airtight glovebox. Fresh gas was prepared using a gas mixing unit with calibrated vaporizers (Draeger, Lübeck, Germany). Fresh gas flow, after equilibration of the atmosphere inside the box with high flow rates, was 5 litre min$^{-1}$ during the experiments. Inside the glovebox, samples were kept at 37 °C with a heated aluminium block. To maintain the amount of evaporated water from the samples low, tubes were sealed with gas-permeable parafilm during all incubations. Volatile delivery under the hood was monitored continuously at the site of the sample tubes by a multi-gas analyser (Capnomac Ultima, Datex, Sweden).

Before filling the polypropylene tubes (diameter 10 mm) and adding leucocytes, Dulbecco's PBS was equilibrated with the anaesthetic inside the glovebox by bubbling fresh gas through for 30 min at 37 °C. The leucocyte-rich plasma was suspended 1:50 (20 $\mu$l of leucocytes and 980 $\mu$l of PBS) in pre-equilibrated Dulbecco's PBS and incubated for 20 min at 37 °C. The leucocytes were loaded with the fluorogenic substrates DHR and SNARF1/AM for 10 min. Cells were pre-exposed to the volatile anaesthetics for 30 min. The final concentrations were 1 $\mu$mol litre$^{-1}$ for DHR and 0.2 $\mu$mol litre$^{-1}$ for SNARF1/AM. Thereafter, FMLP or PMA (10 $\mu$l) at a final concentration of 100 nmol litre$^{-1}$ were added to initiate $H_2O_2$ generation. After 15 min of incubation at 37 °C the reaction was stopped on ice. Dead cells were counterstained with PI (10 $\mu$l) at a final concentration of 30 $\mu$mol litre$^{-1}$. Samples were stored on ice in the dark and measured within 1 h. For evaluation of recovery of neutrophil function, the assay was repeated sequentially for both unexposed control and exposed samples: during exposure and 0.5 h, 1 h and 2 h after the end of exposure.

For analysis we used a FACScan flow cytometer (Becton Dickinson, San José, CA, USA) with argon-ion laser excitation at 488 nm, measuring $10^4$ cells of each stained sample. Data were acquired and processed using LYSIS-II software provided by the cytometer manufacturer. In order to obtain absolute calibration of the fluorescence measurements the arbitrary fluorescence units of the cytometer were transformed into molecule equivalent of soluble fluorochrome (MESF) units. Therefore, after each experiment five populations of standard beads (Quantum 26) with a known content of fluorochrome were measured and a linear regression line was calculated. The MESF units were used for absolute quantification of cellular fluorescence, allowing inter-assay and inter-laboratory comparison of data. Dead cells were assessed by their PI fluorescence (above 600 nm). Leucocyte esterase activity, characteristic for viable cells, was determined based on SNARF1-related orange fluorescence. SNARF1/AM is cleaved in vital leucocytes by esterases to fluorescent SNARF1. Neutrophils were identified by their typical side scatter light (SSC) and forward scatter light (FSC) patterns. SSC depends on the granularity of cells, whereas FSC is related to the size of cells.

### GAS CHROMATOGRAPHY/MASS SPECTROMETRY

For assessment of the concentrations of volatile anaesthetics in the fluid phase of our experiments, we used gas chromatography/high resolution mass spectrometry (GC/HRMS) with a HRGC Mega 2 series (Fisons Instruments SpA, Rodano, Italy). Elution was performed on a 20 m×0.27 mm glass capillary column coated with a 2.1-$\mu$m film of PS 090 (Petrarch Systems Inc., Bristol, PA 19007, USA). The carrier gas was hydrogen at a head pressure of 30 kPa (linear flow rate 0.3 m $s^{-1}$). Samples of 0.75 µl were injected into the split injector (temperature 250 °C, split ratio 1:20); oven temperature was kept at an ambient temperature of 24 °C. The mass spectrometer MAT 95 (Finnigan MAT, Bremen, Germany) was run in electron impact mode at 70 eV electron energy (ion source temperature 180 °C). The mass resolution $m/\Delta m$ was set to 7500; the multiplier voltage was 1.4 kV. Typical ions were recorded by single ion monitoring (SIM) using perfluorotributylamine and carbon dioxide, respectively, as references; cycle time was 0.2 s. Quantification was based on signal areas in the mass chromatograms.

### STATISTICAL ANALYSIS

All data are presented as mean (SD) and range. Analysis of variance and the Student–Newman–Keuls test for multiple pairwise comparison at a significance level of $P<0.05$ were used to compare controls and drug-exposed samples. MAC was designated as the independent variable for analysis of variance to evaluate the effects of different concentrations of volatile anaesthetics. To test the significance of differences in the recovery kinetic data, the Student's *t* test was used. We compared mean fluorescence of unexposed controls processed in parallel with volatile anaesthetic-exposed aliquots.

## Results

Figure 1A shows flow cytometric analysis of resting, non-stimulated leucocytes, whereas figure 1B displays the heterogenous reaction of neutrophils on FMLP stimulation. In contrast, the PMA-induced reaction of all cells was homogenous (fig. 1C). The percentage of reacting and non-reacting neutrophils is given on the left of each dot plot. The percentage of dead cells was lower than 0.1% independent of drug exposure or stimulation.

In the presence of halothane the reactive oxygen derivative generation of neutrophils and monocytes was significantly reduced. At 1 MAC mean fluorescence was 50% compared with control (fig. 1D). In the presence of enflurane (2 MAC), $H_2O_2$ generation reached only 60% of control (table 1). The decreased $H_2O_2$ production correlated with a decreased number of reacting neutrophils. Percentages of neutrophils reacting on FMLP stimulation are given in table 2. The effects observed in the presence of halothane and enflurane were also visible with sevoflurane, although the decrease in $H_2O_2$ production was not significant. Isoflurane did not interfere with neutrophil reaction on FMLP stimulation.

In contrast with all other anaesthetics, the oxidative response after stimulation was enhanced in the presence of desflurane. Both mean fluorescence and percentage of neutrophils responding with a

*Table 1* Influence of different concentrations of volatile anaesthetics on neutrophil oxidative response. Hydrogen peroxide production after stimulation with FMLP or PMA is given as $10^3$ molecule equivalents of soluble fluorochrome (MESF) units (mean (SD)) of nine independent experiments (donors)). $^*P<0.05$, $^{**}P<0.01$

| | FMLP 100 nmol $litre^{-1}$ | | | | PMA 100 nmol $litre^{-1}$ | |
|---|---|---|---|---|---|---|
| Concentration | Control | 0.5 MAC | 1 MAC | 2 MAC | Control | 2 MAC |
| Halothane | 133 (47) | 76 (38)* | 63 (47)** | 80 (51)* | 6972 (891) | 7443 (1666) |
| Enflurane | 152 (51) | 111 (45) | 101 (38) | 92 (35)** | 6556 (666) | 7189 (1225) |
| Sevoflurane | 146 (45) | 111 (35) | 102 (41) | 102 (19) | 6469 (1052) | 7296 (940) |
| Isoflurane | 137 (16) | 108 (41) | 111 (47) | 133 (45) | 6327 (1011) | 7881 (1427) |
| Desflurane | 136 (35) | 125 (33) | 154 (54) | 226 (47)** | 6328 (751) | 6187 (617) |

*Table 2* Influence of different concentrations of volatile anaesthetics on the percentage of respiratory burst positive neutrophils FMLP stimulation. Results are expressed as the percentage of reacting neutrophils from all neutrophils (mean (SD) of nine independent experiments (donors)). $^*P<0.05$, $^{**}P<0.01$

| | FMLP 100 nmol $litre^{-1}$ | | | |
|---|---|---|---|---|
| Concentration | Control | 0.5 MAC | 1 MAC | 2 MAC |
| Halothane | 69 (10) | 57 (7) | 47 (21)* | 55 (17) |
| Enflurane | 54 (12) | 43 (19) | 33 (9)* | 28 (12)** |
| Sevoflurane | 69 (10) | 61 (8) | 61 (16) | 53 (13)** |
| Isoflurane | 66 (15) | 54 (13) | 53 (17) | 58 (14) |
| Desflurane | 55 (7) | 51 (8) | 51 (8) | 67 (12)* |

*Table 3* Recovery of $H_2O_2$ production after FMLP stimulation following exposure to different volatile anaesthetics at 1 MAC for 30 min. Ratio of fluorescence between exposed and unexposed cells from five independent experiments (mean (SD)). $^*P<0.05$, $^{**}P<0.01$

| Time after exposure | 0 h | 0.5 h | 1 h | 2 h |
|---|---|---|---|---|
| Halothane | 0.46 (0.09)** | 0.73 (0.11)* | 0.92 (0.12) | 0.93 (0.08) |
| Enflurane | 0.67 (0.13) | 0.80 (0.21) | 0.96 (0.13) | 0.90 (0.14) |
| Sevoflurane | 0.76 (0.12) | 1.03 (0.18) | 0.97 (0.16) | 0.83 (0.13) |
| Isoflurane | 0.77 (0.05) | 0.77 (0.14) | 0.91 (0.17) | 0.78 (0.11) |
| Desflurane | 1.08 (0.22) | 0.73 (0.14)* | 0.70 (0.10)* | 0.78 (0.10) |

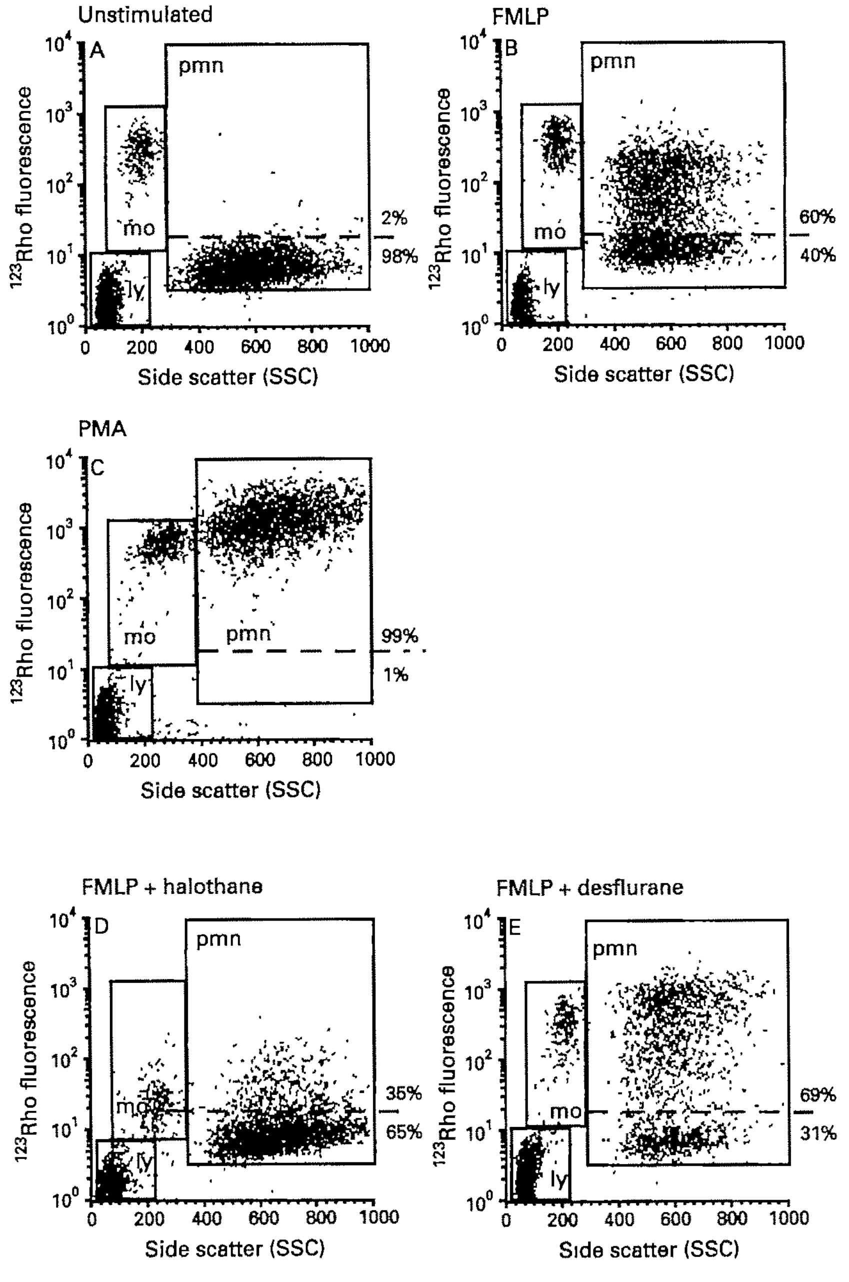

*Figure 1* Flow cytometric analysis of intracellular $H_2O_2$ of 10 000 leucocytes from a representative experiment. The *X*-axis indicates the side scatter (SSC) of leucocytes as a marker of cellular granularity, while the *Y*-axis represents $H_2O_2$ production (rhodamine-123 ($^{123}$Rho) fluorescence) in arbitrary units (neutrophils (pmn), monocytes (mo), lymphocytes (ly)). A: Unstimulated cells; B: cells stimulated with FMLP 100 nmol litre$^{-1}$; C: cells stimulated with PMA 100 nmol litre$^{-1}$; D and E: cells stimulated with FMLP 100 nmol litre$^{-1}$ in the presence of halothane (1 MAC) and desflurane (2 MAC). B serves as a control for D and E. The ratio between reacting and non-reacting cells is given to the right of each dot plot.

respiratory burst reaction were increased compared with controls (fig. 1E, tables 1, 2).

Recovery data are given as the ratio between fluorescence of the exposed and non-exposed samples (table 3). Significant differences between control and drug exposed samples were found for halothane up to 30 min after exposure. Desflurane exposed neutrophils showed transient depression of respiratory burst activity on FMLP stimulation. The impairment lasted less than 2 h.

By GC/HRMS the following buffer/gas partition coefficients and concentrations of volatile anaesthetics for 37 °C and 1 MAC were confirmed: halothane 0.663 and 0.24 (0.01) mmol litre$^{-1}$, enflurane 0.548 and 0.42 (0.02) mmol litre$^{-1}$, isoflurane 0.438 and 0.24 (0.01) mmol litre$^{-1}$, sevoflurane 0.370 and 0.33 (0.01) mmol litre$^{-1}$ and desflurane 0.234 and 0.63 (0.03) mmol litre$^{-1}$. Equilibration was complete after 10 min for all anaesthetics. Ten minutes after removal of the anaesthetic, concentrations in the fluid phase decreased to less than 2% of the initial concentration. The relationship between fluid- and gas-phase concentration was linear in the range relevant to this study.

## Discussion

In this in *vitro* study we have investigated the ability of human neutrophils to form reactive oxygen products after FMLP stimulation during and after exposure to volatile anaesthetics.

Unlike other investigators we used MAC-related concentrations in order to compare equipotent concentrations of anaesthetics. The measured buffer/gas partition coefficients were lower than those coefficients given for blood by other authors and met the coefficients published for saline.[10–12] This may lead to underestimation of the effects presented in this report. In terms of molarity, the MAC-derived differences in concentration were smaller in the fluid phase than in the gas phase of the experiment. For example, 1 MAC of halothane (0.8 vol%) corresponded to 0.24 mmol $litre^{-1}$, whereas 1 MAC of desflurane (6.0 vol%) was only 0.63 mmol $litre^{-1}$.

The small amounts of intracellular $H_2O_2$ generated after stimulation were assessed by quantifying the intracellular oxidation of the indicator dye dihydrorhodamine-123 to rhodamine-123.[13] The former is a non-fluorescent and membrane-permeable fluorogenic substrate whereas the latter oxidation product emits green light (510–530 nm) on excitation.[14] This method has several advantages over those used previously for quantifying neutrophil oxidative function. First, purification of neutrophils, which often leads to artefactual activation of cells, is unnecessary. Second, flow cytometric results are not affected by variations in concentration of neutrophils in the assay, as each individual neutrophil is measured and not the average response of all those assayed. Thus we can show the heterogenous response of neutrophils in an all-or-none reaction after stimulation; only a subset of all neutrophils respond with the respiratory burst reaction on FMLP stimulation while the others remain resting (fig. 1B).

In our study, halothane and enflurane caused a reversible decrease in the formation of $H_2O_2$, which is in accordance with the results of other investigators.[2–7] This inhibition was characterized by a decrease in production of respiratory burst products per neutrophil, and reduction in the number of neutrophils recruited for respiratory burst. Desflurane enhanced the neutrophil response significantly, and a transient decrease in neutrophil oxidative burst activity ensued after removal of anaesthetic. The increased activity not only correlated with increased recruitment of neutrophils, but also enhanced intracellular $H_2O_2$ per cell. Enhanced neutrophil function in the presence of isoflurane has also been shown by Erskine and James[4] and by Nakagawara and colleagues[5] for a concentration corresponding to 2 MAC. The reported effects of isoflurane were not significant in our experiments. Using the receptor independent stimulus PMA, none of the anaesthetics at any concentration had an effect on the oxidative response. The finding of unchanged PMA-induced respiratory burst in the presence of all volatile anaesthetics excludes two potential causes of altered $H_2O_2$ production: scavenging of reactive oxygen derivatives by volatile anaesthetics and direct interference with $H_2O_2$ generating enzymes. Furthermore, Nakagawara and colleagues[5] tested the ability of halothane to scavenge respiratory burst products in cell-dependent and cell-free systems. Neither halothane nor enflurane were able to reduce the amount of generated reactive oxygen products. Thus the significant decrease in $H_2O_2$ production of monocytes in the presence of halothane (fig. 1D) was most likely caused by interference with regulation of the spontaneous oxidative burst of monocytes. This regulation involves signalling pathways different from those mediating neutrophil respiratory burst.

Halothane, enflurane and sevoflurane increased and desflurane decreased the threshold for FMLP-dependent activation such that the number of neutrophils displaying respiratory burst on stimulation declined or increased. PMA activates respiratory burst through the same signal transduction chain as FMLP but at a later activation step. Nakagawara and colleagues[5] investigated the affinity of the FMLP receptor for its agonist in the presence of volatile anaesthetics by measuring the uptake of radioactive labelled FMLP. They found an unchanged affinity of the receptor in the presence of halothane and enflurane. Thus halothane, enflurane and sevoflurane appear to interfere with intracellular signal transduction downstream of the FMLP receptor and upstream of the activation site of PMA.

The bacterial peptide FMLP is a physiological agonist for specific receptors on neutrophils. FMLP has been shown to be a major chemotaxin for neutrophils, and phagocytosis of *Escherichia coli* is mediated mainly by FMLP and its receptor on the neutrophil surface.[15] The concentration of 100 nmol $litre^{-1}$ for FMLP was chosen to allow analysis of the heterogenous response of neutrophils. This concentration also allows comparison with results of other authors.[5] FMLP triggers multiple responses, including chemotaxis, exocytosis of certain enzymes and superoxide generation by the NADPH oxidase complex, the so-called respiratory burst.[1 16–18] Binding of FMLP to the G-protein-coupled receptor induces a temporary increase in phosphatidylinositol-1,4,5-triphosphate, cytosolic calcium, 1,2 diacylglycerol (DAG) and other activators of protein kinase C (PKC).[19 20] Human neutrophils express four PKC isoenzymes ($\alpha$, $\beta$I, $\beta$II, $\zeta$). PKC$\beta$ and $\zeta$ are the most abundant isoforms, while PKC$\alpha$ is hardly detectable. After stimulation with FMLP the PKC isoforms $\beta$I, $\beta$II and $\zeta$ are redistributed from the cytosol to the plasma membrane. PMA is a synthetic analogue of DAG and therefore induces a similar redistribution and activation of PKC, but unlike FMLP the redistribution of PKC is irreversible.[21] The membrane bound form of PKC activates, by intermediate steps, NADPH oxidase. By a single electron transfer, this oxidase transforms molecular oxygen into superoxide anion. Superoxide then dismutates to hydrogen peroxide ($H_2O_2$) inside the phagosomes or in the extracellular space.[1 17] Activation of respiratory burst depends on calmodulin,[22 23] as deduced from experiments using specific antagonists. Calmodulin, an ubiquitous low-molecular-weight protein, regulates the calcium-dependent activity of various enzymes. Périanin, Pedruzzi and Hakim[22] demonstrated that the calmodulin antagonist W-7 dose-dependently enhances and depresses the respiratory burst reaction. Levin and Blanck[24] showed that halothane and isoflurane interfered with the affinity of calmodulin for calcium. Low concentrations of halothane (0.57%) decreased the affinity, whereas higher concentrations (5.7%) significantly increased the ability to bind calcium. The latter effect was found to be irreversible.[24] Isoflurane behaved in a similar way, but halothane was more potent when compared on the basis of MAC values.

These findings may explain the ability of desflurane to enhance and of halothane, enflurane and sevoflurane to lower respiratory burst by interfering with calmodulin, in a manner similar to the known calmodulin antagonist W-7.[22] Thus desflurane might interfere in the same manner as high-dose isoflurane in the experiments of Levin and Blanck,[24] increase the ability of calmodulin to bind calcium and subsequently enhance respiratory burst. This interaction should be irreversible, so that temporary depression of neutrophil function after desflurane exposure might depend on protein synthesis leading to restoration of calmodulin with a normal affinity for calcium. In contrast, halothane or enflurane might decrease the ability of calmodulin to bind calcium and should therefore lead to an immediately reversible inhibition of respiratory burst.

The clinical relevance of impairment of neutrophil function cannot be deduced as our experimental design was not suitable for quantifying clinical effects.

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# Heterogeneous effects of protamine on human mast cells and basophils

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## Summary

To investigate the mechanisms of anaphylactoid reactions to protamine, we have examined the *in vitro* effects of increasing concentrations of protamine ($10^{-6}$–$3\times10^{-4}$ mol litre$^{-1}$) on the release of preformed (histamine and tryptase) and *de novo* synthesized (peptide leukotriene $C_4$ ($LTC_4$) or prostaglandin $D_2$ ($PGD_2$)) mediators from human basophils and mast cells isolated from lung parenchyma, heart, skin and synovial tissues. Protamine $10^{-6}$–$3\times10^{-4}$ mol litre$^{-1}$ induced release of histamine, but not *de novo* synthesis of $LTC_4$ from basophils. At concentrations from $10^{-6}$ to $3\times10^{-4}$ mol litre$^{-1}$ it induced histamine release from human heart (mean 6.5 (SEM 1.5) %), skin (17.7 (4.1) %) and to a lesser extent from synovial mast cells, but not from lung mast cells. Protamine also caused the release of tryptase from heart mast cells (12.8 (3.2) μg/$10^7$ cells), but did not induce *de novo* synthesis of $LTC_4$ and $PGD_2$ from lung and skin mast cells. In these experiments cross-linking of IgE by anti-IgE caused release of $LTC_4$ or $PGD_2$ from human basophils or mast cells. These results demonstrate that protamine acted as an incomplete secretagogue, causing the release of preformed mediators from human basophils and mast cells. (*Br. J. Anaesth.* 1997; **78**: 724–730).

**Key words**
Allergy. Histamine. Pharmacology, protamine.

Protamine sulphate is a basic protein extracted from fish sperm heads.[1] The use of i.v. protamine to reverse heparin anticoagulation has increased in the past decade with the advent of cardiopulmonary bypass technology, cardiac catheterization, haemodialysis and leukapheresis.[2–6] However, protamine may be a major cause of morbidity and mortality in these procedures.[2,4,7–10] During the past decade, reports of adverse reactions associated with i.v. protamine (rash, urticaria, bronchospasm, hypotension and increased pulmonary artery pressure) have also increased.[2–6]

The mechanism(s) by which protamine produces adverse reactions is still not completely understood. It has been suggested that they are caused by complement activation,[5,11,12] inhibition of serum carboxypeptidase,[13] thromboxane production[14,15] and anti-protamine IgE antibody via type I immediate hypersensitivity reactions.[26] It has also been suggested that protamine induces or potentiates histamine release from human basophils and mast cells.[16–18]

Techniques are now available to isolate large numbers of mast cells from human lung parenchyma,[19] heart,[20] skin[21] and synovial tissues.[22] These techniques have led to the demonstration that human basophils and mast cells isolated from different anatomical sites vary markedly in their morphological, biochemical and functional responses.[19–25] These cells differ with respect to the releasing activity of various stimuli and release of different preformed (histamine and tryptase) and *de novo* synthesized mediators (peptide leukotriene $C_4$ ($LTC_4$) and prostaglandin $D_2$ ($PGD_2$)).[26]

Preliminary evidence suggests that human basophils and mast cells may also vary in their histamine releasing capacity when challenged with general anaesthetics. For example, thiopentone activates skin mast cells[24] but not human basophils. It should be emphasized that previous studies have focused on the *in vitro* histamine releasing capacity of protamine[16–18] but have not evaluated its possible effects on *de novo* synthesis of chemical mediators.

To investigate the mechanisms of anaphylactoid reactions to protamine, we have tested *in vitro* to see if protamine induces the release of preformed and *de novo* synthesized mediators from human basophils and mast cells isolated from human heart, lung parenchyma, skin and synovial tissues.

## Materials and methods

### REAGENTS

The following were purchased: 60% $HClO_4$ (Baker Chemical Co., Deventer, The Netherlands); piperazine-N,N'-bis (2-ethanesulphonic acid), hyaluronidase, collagenase type II, chymopapain, elastase type I, synthetic $PGD_2$, (Sigma Chemical Co., St Louis, MO, USA); Hanks balanced salt solution (HBSS) and fetal calf serum (FCS) (Gibco,

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Grand Island, NY, USA); deoxyribonuclease I and pronase (Calbiochem, La Jolla, CA, USA); RPMI 1640 with Hepes buffer 25 mmol litre$^{-1}$, Eagle's minimum essential medium (Flow Laboratories, Irvine, Scotland); Percoll (Pharmacia Fine Chemicals, Uppsala, Sweden); protamine chlorhydrate (Roche SpA, Milan, Italy); ($^3$H)-LTC$_4$ 39.3 Ci mmol$^{-1}$ and ($^3$H)-PGD$_2$ 210 Ci mmol$^{-1}$ (New England Nuclear, Boston, MA, USA). Rabbit anti-human-Fc$\varepsilon$ antibody was kindly donated by Drs Teruko and Kimishige Ishizaka (La Jolla Institute for Allergy and Immunology, La Jolla, CA, USA). The rabbit anti-PGD$_2$ antibody was a generous gift from Dr L. M. Lichtenstein (The Johns Hopkins University, Baltimore, MD, USA). The rabbit anti-LTC$_4$ was kindly provided by Dr E. J. Kusner (Zeneca, Wilmington, DE, USA).[27] The tryptase radioimmunoassay kit (Pharmacia Tryptase RIACT 50, Pharmacia Diagnostics AB, Uppsala, Sweden) was kindly donated by Kabi Pharmacia SpA (Milan, Italy).

### BUFFERS

The Pipes buffer used in these experiments was a mixture of Pipes 25 mmol litre$^{-1}$, NaCl 110 mmol litre$^{-1}$, KCl 5 mmol litre$^{-1}$, pH 7.37, referred to as "P". P2CG contains, in addition to P, CaCl$_2$ 2 mmol litre$^{-1}$ and glucose 1 g litre$^{-1}$ [28]; pH was titrated to 7.4 with sodium bicarbonate. PGMD is: MgCl$_2$•6H$_2$O 0.25 g litre$^{-1}$, DNase 10 mg litre$^{-1}$ and gelatine 1 g litre$^{-1}$ in addition to P, pH 7.37.

### HISTAMINE RELEASE FROM HUMAN BASOPHILS

Informed consent was obtained from all subjects and approximately 50 ml of blood were obtained and diluted into a final concentration of EDTA 0.008 mol litre$^{-1}$ and 1.1% Dextran 70.[26] The procedures for isolation of peripheral blood basophils and *in vitro* mediator release have been described in detail elsewhere.[29] The cell-free supernatant was assayed for histamine with an automated fluorometric technique.[29] Net percentage release was calculated by subtracting histamine released spontaneously from unstimulated samples (mean 3.6 (SEM 0.9) %) from total histamine released from cell samples lysed with 2% perchloric acid.[29] The difference between replicate histamine measurements was less than 10%.

### ISOLATION AND PARTIAL PURIFICATION OF HUMAN HEART MAST CELLS (HHMC)

The heart tissue used in this study was obtained from patients (36–65 yr) undergoing heart transplantation at the Deutsches Herzzentrum, Berlin, mostly for cardiomyopathy. The explanted heart was immersed immediately in cold (4 °C) cardioplegic solution, shipped to Naples by air (4 °C) and processed within 5–18 h of removal. Fat tissue, large vessels and pericardium were removed from the heart (100–400 g). The tissue was minced finely into 2–5-mm fragments, suspended in P buffer (10 ml/g of wet tissue) and washed three times by centrifugation (the first time 150×$g$, 4 °C, 8 min and twice at 150×$g$, 22 °C, 8 min). The heart fragments were filtered through a 150-μm pore Nytex cloth (Tetko, Inc., Elmsford, NY, USA) and incubated for 15 min at 37 °C under constant stirring in P buffer containing 10 mg collagenase/g of wet tissue.[20 28] Three additional cycles of enzymatic digestion were performed, with a new preparation of collagenase each time. After the last enzymatic digestion, the cell suspension was centrifuged (150×$g$, 22 °C, 8 min) and filtered first through a 150-μm pore Nytex cloth and then through a 60-μm pore Nytex cloth to remove large particles and large cells (mostly myocytes). Lastly, cells were washed twice in PGMD (P 25 mmol litre$^{-1}$, NaCl 110 mmol litre$^{-1}$, KCl 5 mmol litre$^{-1}$, Mg 1 mmol litre$^{-1}$, gelatin 1 g litre$^{-1}$, DNase 20 mg litre$^{-1}$; pH 7.37) by centrifugation at 150×$g$, 22 °C for 8 min. Cell pellets were resuspended in 250 ml of P buffer containing 2% BSA and centrifuged (25×$g$, 22 °C, 2 min) to remove sedimented myocytes.[18] Myocytes (>100 μm long) were pelleted and discarded; supernatants containing endothelial cells, fibroblasts and mast cells were then collected and centrifuged (150×$g$, 22 °C, 8 min). At this stage of purification, Alcian blue-positive cells amounted to <1% of the total cells. HHMC were partially purified by flotation through a discontinuous Percoll gradient prepared by mixing 9 parts Percoll and 1 part 10×P solution. This mixture was then diluted with isotonic P to give Percoll concentrations of 40, 50, 60, 70, 80 and 90%. The cell suspension was overlaid on the Percoll gradient in 50-ml polypropylene tubes and the mixture centrifuged at 350×$g$, 22 °C, for 20 min. The cells found at the interface between the 60–70% and 70–80% fractions were removed and washed twice with P. Mast cells in these populations ranged from 0.1 to 16%, with an average of 14.3 (2.4) %. The enzymatic dispersion of tissue yields ranged between 2 and 6×10$^4$ mast cells per gram of heart tissue.

### PURIFICATION OF HUMAN LUNG MAST CELLS (HLMC)

Human lung tissue (20–80 g) was obtained from patients undergoing thoracotomy and lung resection, mostly for lung cancer. General anaesthesia was induced using the following drugs: droperidol with fentanyl and atropine (premedication); droperidol with fentanyl, thiopentone, suxamethonium and pancuronium (anaesthesia). Lung parenchymal mast cells were isolated as described previously.[19] This technique yielded between 3 and 8×10$^5$ mast cells/g of lung tissue, and purities ranged between 1% and 8%.[19]

### PURIFICATION OF HUMAN SKIN MAST CELLS (HSMC)

Skin (15–65 g) was obtained from either mastectomies for breast cancer or elective cosmetic surgery procedures. General anaesthesia was induced using the following drugs: thiopentone, pancuronium, atropine, fentanyl, ethrane or fluorane. Tissue was placed immediately in Eagle's MEM at 4 °C and used within 1 h. HSMC were isolated as described previously.[21 24] This technique yielded between 1 and $7\times10^5$ mast cells/g of wet tissue, and purities ranged between 1% and 4%.

### PURIFICATION OF HUMAN SYNOVIAL MAST CELLS (HSYMC)

Synovial tissue (22–35 g) used in this study was obtained from patients (27–66 yr) with osteoarthritis or rheumatoid arthritis, undergoing synovectomy at the Division of Orthopaedic Surgery. Extradural anaesthesia was induced with mepivacaine i.v. and atropine, fentanyl and benperidol were given systemically. Resected joint tissue was placed immediately in Eagle's MEM at 4 °C and processed within 2 h of removal using a technique described recently.[22] Fat, cartilage and fibrous tissue were removed, and the tissue was minced finely with scissors into 2–5-mm fragments, suspended in P buffer (10 ml/g of wet tissue) and washed twice by centrifugation at $150\times g$ for 8 min at 4 °C and then at 22 °C. The minced synovium was incubated for 45 min at 37 °C in a shaking water bath with chymopapain 1 mg $ml^{-1}$ and pronase 0.5 mg $ml^{-1}$ in 1 ml of Tyrode's buffer/g synovial tissue. Fragments of remaining tissue were digested for another 45 min at 37 °C with collagenase 1 mg $ml^{-1}$. The resulting cell suspensions were pooled, filtered twice through 200-μm pore Nytex cloth (Tetko, Elmsford, NY, USA), centrifuged at $200\times g$, 22 °C for 8 min, and washed twice with P buffer. Cells were washed three times in P and resuspended in P2CG. This technique yielded between 1 and $9\times10^5$ mast cells/g of wet tissue, and purities ranged between 1% and 8%.

### MEDIATOR RELEASE FROM HUMAN MAST CELLS

Mast cells (approximately $3\times10^4$ cells per tube) were resuspended in P2CG, and 0.3 ml of the cell suspension was placed in 12×75 mm polyethylene tubes and warmed to 37 °C; 0.2 ml of each pre-warmed releasing stimulus was added, and incubation was continued at 37 °C for 30 min.[26 29] At the end of this step, the reaction was stopped by centrifugation at $1000\times g$, 22 °C for 2 min, and the cell-free supernatants were stored at −70 °C for subsequent assay of histamine, tryptase, $LTC_4$ and $PGD_2$ content. The cell-free supernatants were assayed for histamine with an automated fluorometric technique.[29] To calculate histamine release as a percentage of total cellular histamine, "spontaneous" release from mast cells (2–12% of the total cellular histamine) was subtracted from both numerator and denominator. The total histamine content in mast cells was obtained by cell lysis with 8% $HClO_4$.[24–26] All values are based on the means of duplicate or triplicate determinations. Replicates differed from each other by less than 10% in histamine content.

### RIA OF TRYPTASE, $LTC_4$ AND $PGD_2$

Total tryptase content was assessed by lysis induced by incubating cells with 0.1% of Triton X-100. Tryptase was analysed by a solid-phase radioimmunoassay (Pharmacia Tryptase RIACT 50).[20 26] $PGD_2$ was analysed on 100-μl fractions obtained from the supernatant fluids. The samples were stored at −70 °C. $LTC_4$ and $PGD_2$ were analysed by RIA within 18 h of the experiment to minimize degradation of the compounds.[23]

### STATISTICAL ANALYSIS

Results are mean (SEM). Statistical analysis was performed by two-way non-parametric analysis of variance (Friedman's chi-square test). The extended Tukey test was used for multiple comparisons. The level of statistical significance was $P<0.05$.[30]

## Results

In the first series of experiments we evaluated the effects of increasing concentrations ($10^{-6}$–$3\times10^{-4}$ mol $litre^{-1}$) of protamine on histamine release from human basophils. Protamine caused concentration-dependent histamine release from basophils from 11 normal donors (table 1). In one experiment, protamine released less then 5% of histamine content but in all other experiments release varied from 5% to 26%. The release caused by protamine reached a plateau between $10^{-5}$ and $3\times10^{-5}$, with less release above these concentrations. Anti-IgE, used as a

*Table 1* Effect of increasing concentrations of protamine on histamine release from human basophils

| Experiment No. | Histamine release (%) | | | | | |
|---|---|---|---|---|---|---|
| | Protamine (mol $litre^{-1}$) | | | | | |
| | $10^{-6}$ | $3\times10^{-6}$ | $10^{-5}$ | $3\times10^{-5}$ | $10^{-4}$ | $3\times10^{-4}$ |
| 1 | 0 | 1 | 3 | 8 | 15 | 16 |
| 2 | 0 | 0 | 1 | 4 | 5 | 4 |
| 3 | 5 | 8 | 14 | 3 | 0 | 0 |
| 4 | 4 | 1 | 9 | 14 | 8 | 3 |
| 5 | 0 | 0 | 4 | 9 | 4 | 4 |
| 6 | 0 | 2 | 14 | 14 | 6 | 5 |
| 7 | 0 | 2 | 12 | 16 | 9 | 6 |
| 8 | 0 | 3 | 26 | 18 | 9 | 8 |
| 9 | 0 | 2 | 16 | 17 | 12 | 8 |
| 10 | 3 | 3 | 5 | 3 | 3 | 5 |
| 11 | 1 | 1 | 3 | 2 | 1 | 1 |
| Mean (SEM) | 1.2 (0.5) | 2.1 (0.6) | 9.7 (2.3) | 9.8 (1.9) | 6.5 (1.4) | 5.5 (1.3) |

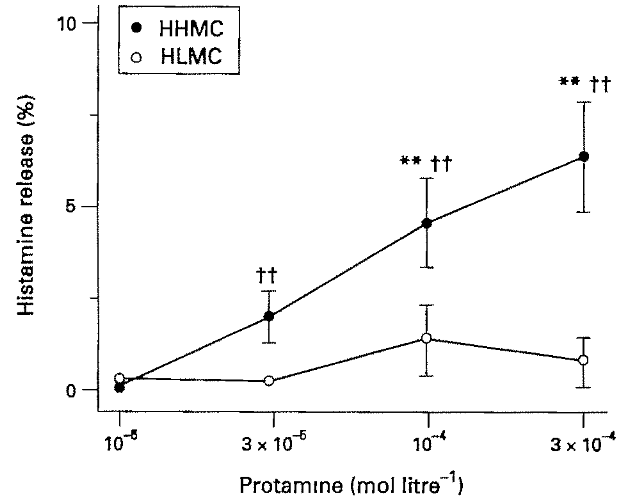

*Figure 1* Effect of increasing concentrations of protamine on release of histamine from HHMC and HLMC. Results are mean (SEM) of 11 (HHMC) or nine (HLMC) different donors. Error bars are not shown when graphically too small $^{**}P<0.01$ compared with spontaneous release; $^{\dagger\dagger}P<0.01$ compared with histamine release induced by protamine from HLMC.

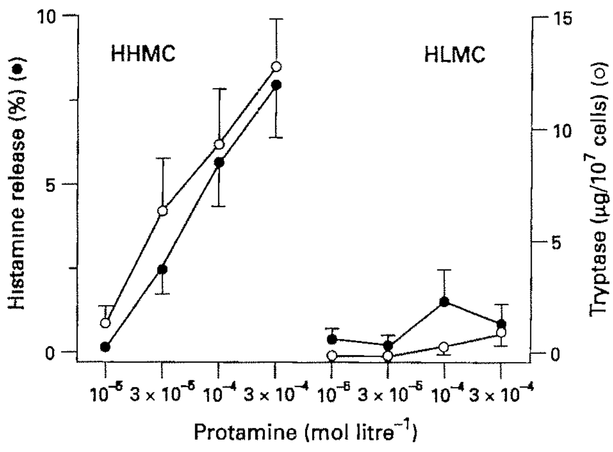

*Figure 2* Effect of increasing concentrations of protamine on histamine and tryptase release from HHMC and HLMC. Results are mean (SEM) of four (HHMC) or five (HLMC) different donors. Error bars are not shown when graphically too small.

positive control in these experiments, induced 28.9 (5.4) % of histamine release. There was no correlation between the maximum release caused by protamine and anti-IgE ($r_s$=0.01; ns). Cell viability in the presence of protamine was always ≥95% as detected by trypan blue exclusion.[28]

In the second series of experiments we compared the effect of protamine on histamine release from HHMC and HLMC. Protamine $10^{-5}$– $3\times10^{-4}$ mmol litre$^{-1}$ induced histamine release from HHMC in a concentration-dependent manner (fig. 1) with maximum release between 3% and 17% (8.8 (1.4) %) ($P<0.01$ compared with spontaneous release). In none of nine HLMC preparations did protamine induce the release of more than 5% of histamine content (fig. 1).

In view of the functional heterogeneity of human mast cells isolated from different anatomical sites,[20] [22–26] [28] we evaluated the effects of increasing concentrations ($10^{-5}$–$3\times10^{-4}$ mmol litre$^{-1}$) of protamine on histamine release from mast cells from skin and synovial tissues. These concentrations of protamine induced histamine release from HSMC (table 2) and to a lesser extent from HSyMC (table 3). The maximum release varied between 7% and 25% (HSMC) and 12% and 13% (HSyMC).

Tryptase is a neutral protease that is a selective marker for mast cells.[31] The secretory granules of all mature human mast cells contain large amounts (approximately 24.2 (4.3) μg/$10^6$ HHMC of tryptase).[20] [22] We investigated if activation of HHMC with protamine caused release of tryptase in addition to histamine. Tryptase was released in parallel with histamine from HHMC whereas protamine did not induce release of histamine and tryptase (<5%) from HLMC in three experiments (fig. 2).

*Table 2* Effect of increasing concentrations of protamine on histamine release from HSMC

| | Histamine release (%) | | | | | |
|---|---|---|---|---|---|---|
| | Protamine (mol litre$^{-1}$) | | | | | |
| Experiment No. | $10^{-6}$ | $3\times10^{-6}$ | $10^{-5}$ | $3\times10^{-5}$ | $10^{-4}$ | $3\times10^{-4}$ |
| 1 | 0 | 1 | 18 | 23 | 23 | 25 |
| 2 | 0 | 1 | 4 | 9 | 16 | 23 |
| 3 | 0 | 2 | 8 | 8 | 6 | 16 |
| 4 | 4 | 7 | 7 | 7 | 7 | 7 |
| Mean (SEM) | 1.0 (1.0) | 2.8 (1.4) | 9.2 (3.0) | 11.8 (3.8) | 13.0 (4.0) | 17.7 (4.1) |

*Table 3* Effect of increasing concentrations of protamine on histamine release from HSyMC

| | Histamine release (%) | | | | | |
|---|---|---|---|---|---|---|
| | Protamine (mol litre$^{-1}$) | | | | | |
| Experiment No | $10^{-6}$ | $3\times10^{-6}$ | $10^{-5}$ | $3\times10^{-5}$ | $10^{-4}$ | $3\times10^{-4}$ |
| 1 | 0 | 0 | 0 | 0 | 0 | 13 |
| 2 | 0 | 0 | 0 | 0 | 4 | 10 |
| 3 | 0 | 0 | 0 | 0 | 2 | 12 |
| Mean (SEM) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (1.1) | 11.6 (0.8) |

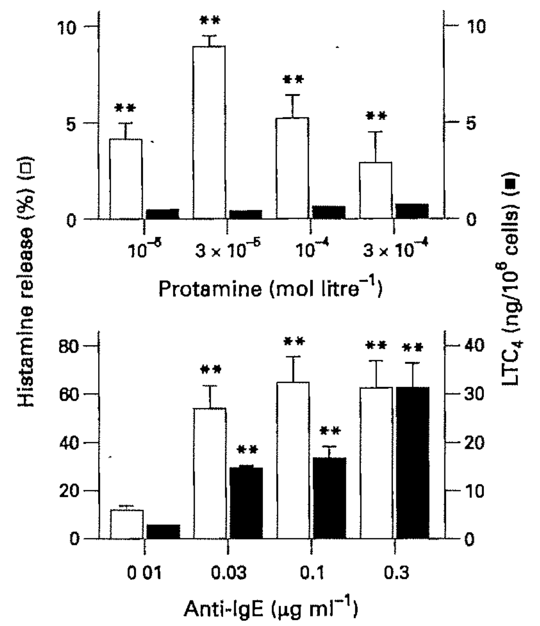

*Figure 3* Effect of increasing concentrations of protamine and anti-IgE on release of histamine and LTC$_4$ from human basophils. Results are mean (SEM) of three experiments. Error bars are not shown when graphically too small. **$P<0.01$ compared with spontaneous release.

Different experimental models have shown that some of the adverse effects of protamine are caused by generation of eicosanoids.[32,33] We therefore compared production of the newly formed lipid mediators from human basophils and mast cells activated by protamine $10^{-5}$–$3 \times 10^{-4}$ mmol litre$^{-1}$ and anti-IgE $10^{-2}$–$3 \times 10^{-1}$ µg ml$^{-1}$. In this group of experiments protamine induced concentration-dependent release of histamine from basophils, but did not stimulate *de novo* synthesis of LTC$_4$ by these cells (fig. 3). Anti-IgE stimulated release of large amounts of LTC$_4$. Protamine also did not induce *de novo* synthesis of PGD$_2$ or LTC$_4$ from HHMC and HSMC, whereas anti-IgE stimulated the release of these eicosanoids (data not shown).

## Discussion

Our results indicate that protamine is an incomplete secretagogue inducing only release of preformed mediators (histamine and tryptase) from human basophils and mast cells without stimulating *de novo* synthesis of eicosanoids. Protamine activated not only peripheral blood basophils, but also mast cells isolated from human heart, skin and synovial tissues, but not from lung parenchyma.

Intravascular administration of high concentrations of protamine is used increasingly to reverse heparin anticoagulation during cardiac catheterization,[4] cardiothoracic and vascular surgical procedures[34,35] and after dialysis[36] and leukapheresis.[37] I.v. protamine can cause acute reactions such as rash, urticaria, bronchospasm, hypotension, cardiovascular collapse, pulmonary hypertension and even death.[2,4,7-9] These adverse reactions are thought to be caused by multiple mechanisms, including anaphylactic[2-6] and anaphylactoid reactions.[11-14,16-18] Intravascular administration of protamine causes rapid and massive exposure of basophils to this agent. It is therefore likely that the release of histamine from peripheral blood basophils might at least partly explain some of the adverse effects of protamine in some patients.

Intravascularly administered compounds rapidly expose circulating basophils and tissue mast cells to very high concentrations that tend to decline according to their pharmacokinetics. Thus we investigated the effects of a wide range of concentrations of protamine which must include concentrations reached during intravascular administration of the compound. The percentage of histamine release from basophils caused by protamine varied greatly from donor to donor, presumably because of the influence on basophil releasibility.[19,23,38] This may partly explain the wide variability of protamine-induced adverse effects in patients given this drug intravascularly.[6] At first sight, the bell shape of the dose–response curve of protamine on release of histamine from basophils might be surprising. However, other stimuli (anti-IgE, antigens, etc.) can produce a similar dose–response curve.[20]

Although it has been demonstrated in different experimental models that the adverse reactions to protamine are to some extent caused by synthesis of eicosanoids and other lipid mediators,[32,33] protamine did not induce release of LTC$_4$ and PGD$_2$ from human basophils and mast cells *in vitro*. Possibly *in vivo* protamine induces the release of lipid mediators from other cells.

Radiocontrast media, which can cause anaphylactoid reactions, also act as incomplete secretagogues on human basophils and mast cells[26] and pretreatment with histamine H$_1$ and H$_2$ receptor antagonists reduces the incidence and severity of adverse reactions to these agents.[39] In the light of our results, it might be appropriate to investigate if these antagonists also reduce the incidence of anaphylactoid reactions to protamine.

Protamine caused a concentration-dependent release of tryptase from HHMC, HSMC and HSyMC. This neutral protease, present in the cytoplasmic granules of all human mast cells,[20,22,31] can activate complement leading to the formation of anaphylatoxins (C3a and C5a).[40] Complement activation and C3a formation can occur during *in vivo* administration of protamine[11-14] and tryptase release from mast cells might therefore contribute, as an amplification factor, to the pathogenesis of the generalized reactions to protamine, through activation of the complement system. Tryptase has a longer half-life than histamine in plasma.[31] Therefore, it may be useful to measure plasma concentrations of tryptase in order to identify adverse reactions caused by protamine in humans.

Our results showed that protamine can induce release of vasoactive and proinflammatory mediators from HHMC *in vitro*. Coronary artery spasm, hypotension and shock can occur during intravascular administration of protamine.[8,9] Mast cells have been demonstrated clearly within human heart tissue,[20,28] around coronary vessels and in the shoulder region of atherosclerotic human coronary vessels.[41] During intravascular administration of protamine, cardiac mast cells are likely to be exposed to high concentrations and our findings suggest that *in vivo* they can thus be activated to release histamine, tryptase and possibly other mediators. Histamine exerts significant cardiovascular effects in humans[42] and vasoactive mediators released locally from coronary and cardiac mast cells might therefore contribute to the pathogenesis of severe adverse reactions to protamine.

Unlike HHMC and HSMC, HLMC were not activated by protamine *in vitro*. However, transient increases in pulmonary artery pressure are frequent when protamine is administered i.v.[7 14] It is therefore possible that the pulmonary reactions to protamine involve alternative mechanisms such as direct activation of basophils, tryptase-mediated formation of anaphylatoxins that in turn activate C5a receptors on HSMC[18 23] and HHMC,[20] or other unknown mechanisms. Our results were obtained with preparations of mast cells isolated from different tissues of patients receiving several drugs before and during surgical procedures. Consequently, we cannot exclude the possibility that some of the heterogeneous effects of protamine on the release of mediators from mast cells isolated from different tissues might be influenced by the *in vivo* treatment of the cell donors.

In conclusion, these findings suggest that protamine selectively activated different types of human mast cells and basophils, acting as an incomplete secretagogue. These results are of interest for several reasons. They contribute to a better understanding of the pathogenesis of immediate generalized reactions caused by rapid injection of protamine and they also suggest that anti-$H_1$ and anti-$H_2$ blockers might be useful in attenuating anaphylactoid reactions to this substance. Finally, they indicate that measurements of plasma tryptase might be useful to identify adverse reactions.

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REVIEW ARTICLE

# Glutamate: a role in normal brain function, anaesthesia, analgesia and CNS injury

M. J. HUDSPITH

Glutamate is the major excitatory amino acid (EAA) neurotransmitter in the central nervous system (CNS).[78] EAA neurones and synapses are distributed widely throughout the CNS,[36 231] but they are concentrated particularly in the hippocampus,[91] the outer layers of the cerebral cortex[91] and the substantia gelatinosa of the spinal cord.[194] Within these regions EAA play key roles in physiological processes including learning and memory (and hence awareness under anaesthesia), central pain transduction mechanisms and pathological processes such as excitotoxic neuronal injury which follows CNS trauma or ischaemia. Thus an understanding of the role of EAA in the CNS is relevant to normal higher brain function and to anaesthesia, analgesia and intensive care.

A broad spectrum of pharmacological agents which alter EAA-mediated neurotransmission are already available and many more are under development. These include: (i) drugs that specifically target the release of EAA (e.g. the novel antiepileptic drugs felbamate and lamotrigine), (ii) drugs that modify the interactions of EAA with specific receptors (e.g ketamine) and (iii) volatile and i.v. anaesthetic agents which may have a common mechanism of action that, at least in part, involves EAA-mediated neurotransmission. To understand the potential applications of these agents it is necessary to consider first how EAA act at the level of the synapse and the individual neurone. To do so involves a brief outline of EAA receptor subtypes and how their activation affects the postsynaptic neurone. It may then be possible to explain how EAA and their receptors are involved in cognition, anaesthesia, analgesia and neurointensive care and therefore to provide a framework to assess the possible clinical applications of drugs which modify EAA-mediated neurotransmission.

## Excitatory amino acid neurotransmission

A diagrammatic representation of an EAA synapse comprising a presynaptic nerve terminal and a postsynaptic neurone expressing multiple EAA receptor subtypes is shown in figure 1 and described first in terms of presynaptic events and then activation of postsynaptic receptors.

### PRESYNAPTIC EVENTS

Glutamate, synthesized by the deamination of glutamine or via the tricarboxylic acid cycle, is released into the synaptic cleft in response to depolarization of the presynaptic nerve terminal. The release of glutamate from presynaptic terminals (and that of other neurotransmitters), is a $Ca^{2+}$-dependent process regulated by multiple types of $Ca^{2+}$ channel. N-type and P-type $Ca^{2+}$ channels are probably the most important determinants of exocytotic neurotransmitter release from presynaptic nerve terminals throughout the CNS[55] although other channel types (such as Q and R) may also be involved. Importantly, different $Ca^{2+}$ channel types may be involved in the exocytotic release of neurotransmitter from different neurones within the CNS and from different sites in individual neurones.[55] After release of glutamate, binding to specific receptor types described in the following section determines the postsynaptic response.

In common with many other central neurotransmitter systems,[88] the actions of glutamate within the synaptic cleft are terminated by high affinity sodium-dependent uptake. Glutamate transporters are localized in both pre- and postsynaptic neuronal elements together with glial cells.[182] Three, or possibly four, glutamate transporters have been characterized[64 96 164 201] (for a recent review see Malandro and Kilberg[128]), each of which are transmembrane proteins of approximately 60–70 kDa size with $K_m$ values for glutamate in the low micromolar range.

### EXCITATORY AMINO ACID RECEPTORS

Two main subgroups of EAA receptors have been identified: *ionotropic* and *metabotropic* receptors.[191 223] Ionotropic glutamate receptors (*i*Glu-receptors) are so named because such receptors are ligand-operated ion channels (LOC) and a change in membrane permeability to specific cations occurs

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**Key words**
Protein, amino acids, glutamate. Brain, glutamate. Nerve, neurotransmitters. Pain. Anaesthesia, general.

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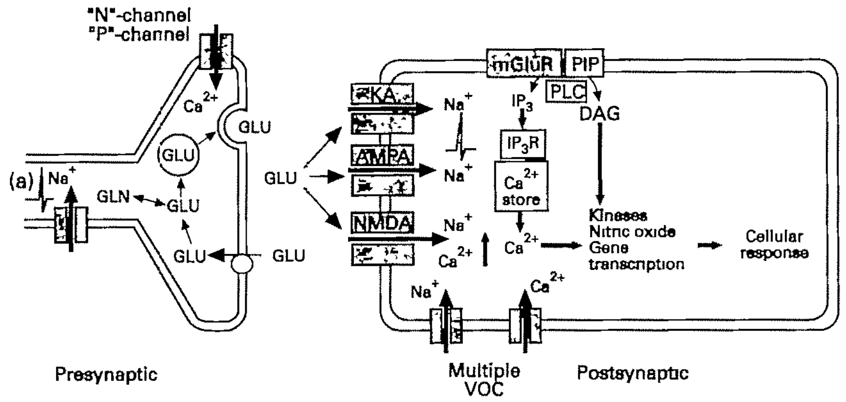

*Figure 1* Schematic representation of an excitatory amino acid (EAA) synapse within the CNS. Glutamate is released from the presynaptic nerve terminal in response to depolarization-dependent $Ca^{2+}$ entry through "N-" or "P-" type voltage-operated $Ca^{2+}$ channels. Glutamate within the synaptic cleft can bind to ionotropic and metabotropic glutamate receptors (mGluR) on the postsynaptic neurone: individual neurones may express multiple glutamate receptor subtypes. Receptor activation evokes a cellular response via increases in intracellular $Ca^{2+}$ and activation of protein kinases. GLU=glutamate; NMDA=*N*-methyl-D-aspartate; KA=kainate; GLN=glutamine; AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; PIP=phosphatidyl-inositol-4,5-bisphosphate; PLC=phospholipase C; $IP_3$=inositol-1,4,5-trisphosphate; $IP_3R$=$IP_3$ receptor; DAG=diacylglycerol; VOC=voltage-operated ion channel; (a)=depolarization and action potential generation.

within a few milliseconds of agonist binding (see below). The *i*Glu-receptor family can be classified pharmacologically according to activation by specific agonists into three subtypes: *AMPA* receptors (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate), *KA* receptors (kainate) and *NMDA* receptors (*N*-methyl-D-aspartate).

The family of metabotropic glutamate receptors (*m*Glu-receptors; for clarity, *m*GluR in fig. 1) are receptors linked to G-proteins that modulate intracellular second messengers such as inositol phosphates and cyclic nucleotides. Their classification is complicated by the lack of ligands showing selectivity for individual *m*Glu-receptor subtypes. However eight *m*Glu-receptor subtypes have been identified by molecular biological techniques (for reviews see Miller,[139] Nicoletti and colleagues,[150] and Pin and Duvoisin[163]); all are members of the 7-transmembrane receptor superfamily and can be further classified according to sequence homology and signal transduction pathways into three groups (see table 1). Whereas activation of *i*Glu-receptors results in a response (i.e. membrane depolarization) within a few milliseconds of agonist binding, the G-protein coupled *m*Glu-receptors evoke changes in neuronal excitation on a time scale of hundreds of milliseconds to seconds.

In contrast to the 7-transmembrane *m*Glu receptor, ionotropic EAA receptors are composed of multiple subunits. At least 16 genes encoding *i*Glu receptor subunits have been characterized (see table 2: for reviews see Seeburg[193] and Sucher and colleagues[203]), and some of these genes (notably those encoding the NMDAR1[56] and GluR1-GluR4[197] subunits) undergo RNA editing producing multiple splice variants. Accordingly, multiple variants of glutamate receptor subtypes are expressed throughout the CNS and can be identified using molecular biological techniques.[83 206 232] However, for the purpose of this review the pharmacological classification listed above will be used. The roles of the *i*Glu-receptor family in systems of relevance to anaesthesia and analgesia are currently better characterized than those of the *m*Glu-receptor family; much of the following therefore concentrates on *i*Glu-receptor mediated mechanisms of neurotransmission.

### *Ionotropic receptors*

When activated, *i*Glu-receptors undergo a conformational change that results in the opening of their

*Table 1* Classification of metabotropic glutamate receptors $m\text{Glu}_1$–$m\text{Glu}_3$ (modified and redrawn from IUPHAR[87] and Nicoletti and colleagues[150]). 4CPG=S-4-carboxyphenylglycine; L-AP4=L-amino-4-phosphonobutanoate; 2R,4R-APDC=2R,4R-aminopyrrolidine-2,4-dicarboxylate; cAMP=cyclic 3',5'-adenosine-monophosphate; DCG-IV=(2S,1'R,2'R,3'R,)-2-(2',3'-dicarboxycyclopropyl)glycine; DHPG=3,5,dihydrophenylglycine; MAP4=methyl-L-AP4; MCCG=2S,1'S,2'S-2-methyl-2-(2'-carboxycyclopropyl)glycine; MPPG=(RS)-α-methyl-4-phosphonophenylglycine; $IP_3$=Inositol 1,4,5 trisphosphate; $I_K$=Voltage-operated $K^+$-channel; $I_{Ca}$=Voltage-operated $Ca^{2+}$-channel

| *m*Glu receptor subtypes | | Agonists | Antagonists | Transduction pathway (G-protein effector) |
|---|---|---|---|---|
| Group 1 | $m\text{Glu}_1$ | DHPG | 4CPG | $\uparrow IP_3$ |
| | $m\text{Glu}_5$ | | | $\downarrow I_K$ |
| Group 2 | $m\text{Glu}_2$ | DCG-IV | MCCG | ↓cAMP |
| | $m\text{Glu}_3$ | 2R,4R-APDC | | $\downarrow I_{Ca}$ (L,N,P channel) |
| | | | | $\uparrow I_K$ |
| Group 3 | $m\text{Glu}_4$ | L-AP4 | MAP4 | ↓cAMP |
| | $m\text{Glu}_{6-8}$ | | MPPG | $\downarrow I_{Ca}$ (N,P channel) |

*Table 2* Classification of ionotropic glutamate receptors (modified and redrawn from IUPHAR[86]). D-AP5=D-amino-5-phosphonopentanoate; AMPA=D,L-α-amino-3-hydroxy-5-methyl-4-isoxalone propionic acid; CGS19755=4-phosphonomethyl-2-piperidine carboxylic acid; KA=kainate; MNQX=5,7-dinitroquinoline-2,3-dione; NBQX=6-nitro-7-sulphamobenzyl(*f*)quinoxaline-2,3-dione; NMDA=*N*-methyl-D-aspartate; NS102=6-cyano-7-nitro-2,3-quinoxalinedione

| *i*Glu receptor subtype | Subunit genes | | Agonist | Antagonists | Transduction pathways |
|---|---|---|---|---|---|
| AMPA | GluR1 | | AMPA | NBQX | ↑$[Na^+]_i$ |
| | GluR2 | | | | (↑$[Ca^{2+}]_i$?) |
| | GluR3 | | | | |
| | GluR4 | | | | |
| KA | GluR5 | | Kainate | NS102 | ↑$[Na^+]_i$ |
| | GluR6 | | | | |
| | GluR7 | | | | |
| | KA1 | | | | |
| | KA2 | | | | |
| NMDA | NR1 | Competitive | NMDA | D-AP5 | ↑$[Ca^{2+}]_i$ |
| | NR2A | site | | CGS19755 | |
| | NR2B | Modulatory | Glycine | 5,7-dichlorokynurenate | |
| | NR2C | site | | MNQX | |
| | NR2D | | | | |

respective ligand-operated channel (LOC). The gating properties and ion flux through *i*Glu-receptor LOC may be modified by the binding of other ligands to modulatory binding sites separate from the glutamate binding site. Activation of *i*Glu-receptors causes transmembrane flux of cations resulting in depolarization of the postsynaptic membrane. Subsequent postsynaptic events may be a direct consequence of cation entry and/or opening of voltage-operated ion channels and further cation entry (see fig. 1).

*AMPA receptors.* AMPA receptor channels consist of homomeric or heteromeric assemblies of GluR1-GluR4 subunits[193] (see table 2); the resultant receptor channel is primarily a $Na^+$ channel with rapid kinetics of activation and deactivation. Such a kinetic profile renders AMPA receptors ideal for mediation of fast excitatory neurotransmission throughout the CNS, and their generally very low $Ca^{2+}$ permeability ensures that this glutamate-activated excitation does not trigger longer term biochemical processes evoked by an increase in intracellular $Ca^{2+}$ concentrations.

All AMPA receptors show onset, offset and desensitization time courses in the order of a few milliseconds, although current:voltage relationships and cation permeability are specifically determined by subunit composition. For example, the normally cation impermeable AMPA receptor channel may permit $Ca^{2+}$ entry if the GluR2 is absent,[81] although whether AMPA receptor-mediated $Ca^{2+}$ entry has physiological relevance is unclear. A second binding site for 2,3 benzodiazepines attenuates the response of the channel to prolonged agonist stimulation and 2,3 benzodiazepines act as non-competitive AMPA antagonists.[51]

*Kainate receptors.* The neurotoxin, kainate (KA), binds to a specific high affinity KA receptor (identified in sensory ganglia) and activates a rapidly desensitizing $Na^+$ channel[82] with similar kinetics to the AMPA receptor. High affinity kainate receptors can be generated *in vitro* from multimeric assemblies of GluR5–7 and KA1 or KA2 subunits[193] (table 2) but again, precise kinetic variables of activation and inactivation are determined by subunit composition. Kainate also binds to the AMPA receptor with a lower affinity resulting in persistent, non-desensitizing activation of the AMPA receptor channel and this effect may overshadow transient high affinity KA receptor responses in central neurones.[193] Currently the distinction between AMPA and kainate receptors is somewhat blurred dependent on classification according to gating or ligand binding, however, activation of either receptor subtype by the endogenous ligand glutamate results in rapid, although transient, depolarization of the postsynaptic membrane.

*NMDA receptors.* The NMDA receptor channel preferentially permits $Ca^{2+}$ entry[119] and the kinetics of this channel are much slower than those of the two preceding types of *i*Glu-receptor with channel opening persisting for several tens or hundreds of milliseconds. NMDA receptors can be reconstituted *in vitro* as heteromeric combinations of the NR1 subunit and one of four NR2 subunits (NR2A-D)[193 203] (table 2). The NR1 subunit common to all NMDA receptors exists in at least eight splice variants,[232] and this together with the four NR2 subunits provide the potential for a vast array of NMDA receptor subtypes to exist within the CNS. As with each of the ionotropic glutamate receptor classes, subunit composition determines the (complex) gating properties of the channel, however caution has been recommended in comparing the pharmacological properties of recombinant NMDA receptors with those of native neurones[203] and no attempt is made in the following to differentiate between NMDA receptor subtypes.

The gating properties of the NMDA receptor channel are complex and subject to modulation at several different sites (fig. 2). In addition to its binding site for EAA such as NMDA or glutamate, the receptor has a second binding site for glycine which facilitates the actions of glutamate or NMDA.[93] However, in the resting (i.e. non-depolarized) state, the NMDA receptor channel is blocked by $Mg^{2+}$ ions at a site deep within the channel itself[133 152] and binding of NMDA or glutamate to the agonist binding site, even in the presence of glycine, does not result in $Ca^{2+}$ entry through the postsynaptic

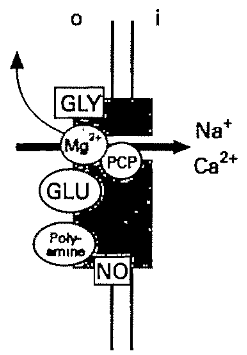

*Figure 2* Schematic representation of the NMDA receptor complex. In the non-depolarized neuronal membrane, binding of glutamate and glycine does not result in $Ca^{2+}$ entry while the ion channel remains blocked by $Mg^{2+}$. Depolarization removes the $Mg^{2+}$ block enabling cation entry. Cation flux is inhibited by agents binding to the phencyclidine site within the ion channel and modulated by agents interacting with the polyamine and redox sites. i= Intracellular; o=extracellular; GLU=glutamate; GLY=glycine; PCP=phencyclidine; NO=redox site.

membrane. Depolarization of the membrane removes the $Mg^{2+}$-mediated channel blockade and $Ca^{2+}$ flux through the channel can then occur. Calcium entry through the NMDA receptor channel can also be modulated by micromolar concentrations of $Zn^{2+}$ ions[132,220] which inhibit channel opening time in a voltage-independent manner.[134] The NMDA receptor channel is subject to further modulation by agents such as dizolcipine (MK-801) that bind to a site (phencyclidine binding site) within the channel itself[92]; binding to this site is enhanced significantly when the channel is activated and such agents (which include the dissociative anaesthetics ketamine and phencyclidine) are known as *open-channel blockers*. Outside the channel are further modulatory sites: these include a polyamine binding site[175] and a redox site[110] where sulphydryl groups of the subunits may interact with nitric oxide (NO) derivatives to modify channel function.

The slow kinetics of dissociation of glutamate from its agonist site (time constants of decay in the order of tens or hundreds of milliseconds), and the necessity of coincident membrane depolarization to permit channel opening enable the NMDA receptor to function as a molecular detection device for near coincident pre- and postsynaptic depolarization. The resultant increase in intracellular $Ca^{2+}$ may trigger sequences of molecular events that lead to longer term changes in neuronal function.

## Excitatory amino acids and anaesthesia

General anaesthetic agents have a broad spectrum of actions; they modify both inhibitory and excitatory neurotransmission at presynaptic and postsynaptic loci within the CNS[67,108,166,176]; nevertheless their precise mode of action remains uncertain and undoubtedly they interact with multiple neurotransmitter systems by a variety of mechanisms.[115]

*Table 3* Anaesthetic effects on EAA neurotransmission. L-GLU, NMDA, AMPA/KA indicates effect on neurone (either depolarisation or $Ca^{2+}$ entry) in response to specific agonist. ↓=inhibition, ↔↓=inhibition at high concentration, ↑=potentiation, ↔=no effect. B=whole brain, C=cerebral cortex, H=hippocampus, Th=thalamus, Sp=spinal cord, O=oocytes expressing human brain mRNA

| Anaesthetic | EAA release | Ref. | L-GLU | Ref. | NMDA | Ref. | AMPA/KA | Ref. |
|---|---|---|---|---|---|---|---|---|
| Isoflurane | ↓ C | [138]<br>[190] | ↓ C | [168] | ↓ C | [24]<br>[168] | ↓ C | [24] |
| | ↓ H | [13]<br>[109]<br>[124] | | | ↔↓ C | [131] | ↓ H | [169]<br>[218] |
| | ↓ Sp | [187] | | | ↓ H | [169]<br>[229] | | |
| | ↔ H | [161] | | | ↓ Sp | [187] | | |
| Enflurane | ↓ C | [138]<br>[190] | — | | ↓ C | [7]<br>[131] | ↓ O | [112] |
| | ↑ B | [79] | | | ↓ O | [112] | | |
| Halothane | ↓ C | [178]<br>[190] | ↓ C | [168]<br>[178] | ↓ C | [7]<br>[131]<br>[168] | ↓ C | [24] |
| | ↔↑ C | [5] | ↔ H | [162] | ↔ C | [24] | ↓ H | [148]<br>[169] |
| | ↓ H | [124]<br>[162]<br>[179] | | | ↓ H | [148]<br>[169] | ↔ H | [162] |
| | ↔ B | [79] | | | ↔ H | [162] | | |
| Methoxyflurane | ↓ C | [177] | ↓ C | [177]<br>[178] | ↓ C | [131] | — | |
| | ↓ H | [179] | | | | | | |
| Diethylether | ↓ C | [177] | ↓ C | [177]<br>[178] | ↓ C | [24]<br>[131] | ↓ C | [24] |
| | ↓ H | [179] | | | ↓ H | [218] | ↔ H | [218] |
| | ↔ B | [79] | | | | | | |
| Trichloroethylene | ↓ C | [177] | ↓ C | [178] | — | | — | |
| Propofol | — | | ↓ B | [15] | ↓ H | [14] | ↔ H | [14] |
| Barbiturate | ↓ C | [33]<br>[140] | ↓ C | [178] | ↓ H | [188] | ↓ C | [24] |
| | ↔ C | [190] | ↓ H | [188] | ↔ H | [218] | ↓ H | [188]<br>[218] |
| | ↓ Th | [100] | | | | | | |

Attempts have been made to produce "unitary theories of anaesthesia" and one proposed mechanism, common to general anaesthetic action is that of potentiation of the inhibitory neurotransmitter γ-amino-butyric acid (GABA) at the $\text{GABA}_A$ receptor $\text{Cl}^-$ channel.[67] However, there is a growing body of evidence that general anaesthetic agents also modify EAA-mediated excitatory neurotransmission in the CNS, and this has important implications with regard to the means by which anaesthetics suppress the responses to, and awareness of, noxious stimuli. The evidence for anaesthetic effects on EAA is reviewed below (data summarized in table 3).

## PRESYNAPTIC EFFECTS OF GENERAL ANAESTHETICS

As stated above, the release of EAA neurotransmitters is dependent on $\text{Ca}^{2+}$ entry into nerve terminals through N-type, P-type and possibly other voltage-operated channels in the presynaptic membrane.[55] Voltage-operated $\text{Ca}^{2+}$ channels are themselves a target of general anaesthetic action and the evidence for their inhibition by volatile and i.v. anaesthetics in a variety of neuronal populations has been reviewed recently.[102] Two studies that specifically examined anaesthetic effects on $\text{Ca}^{2+}$ channel subtypes in hippocampal neurones have shown that halothane, enflurane and isoflurane markedly inhibit multiple $\text{Ca}^{2+}$ channel types at clinically relevant concentrations.[106,202] It should be noted that $\text{Ca}^{2+}$ channel sensitivity to general anaesthetics may vary in different neuronal populations as P-type $\text{Ca}^{2+}$ channels were unaffected by isoflurane in cerebellar neurones[76] but may be sensitive to this agent in hippocampal neurones.[202]

Inhibition of $\text{Ca}^{2+}$ channel function would be expected to reduce the release of EAA and several early studies suggested that both volatile anaesthetics[177,178,179] and barbiturates[33,100,140] could decrease the depolarization-evoked release of EAA neurotransmitters from central neurones. Recent studies have confirmed this effect with the demonstration that both isoflurane[109,124] and halothane[124,162] at clinically relevant concentrations (0.5–2 MAC) markedly inhibit release of glutamate from hippocampal neurones in a dose-dependent manner. Furthermore, data demonstrating inhibition by halothane, enflurane and isoflurane of glutamate release[138,190] associated with reduced $\text{Ca}^{2+}$ entry[138] in cerebral cortical nerve terminals strongly suggest that presynaptic inhibition of glutamate release may be a common property of volatile anaesthetic agents.

The specific sodium-dependent glutamate transporters that limit the synaptic duration of EAA by uptake into both neurones and astroglia have been shown not to be sensitive to clinically relevant concentrations of either volatile or i.v. anaesthetics.[149]

## POSTSYNAPTIC EFFECTS OF GENERAL ANAESTHETICS

When postsynaptic effects are considered, it is clear that volatile and i.v. anaesthetic agents have in general, inhibitory effects on the excitatory responses of CNS neurones to exogenously applied EAA agonists (see table 1). Inhibition of each of the *i*Glu-receptor subtypes has been reported by a number of investigators,[14,148,169,188,218,229] however, subtype specific effects on *i*Glu-receptor function have not been consistent. This may reflect the different methodologies used in these studies; most notably this applies to halothane which under different conditions may either inhibit[148,169] or have no effect[162] on hippocampal NMDA receptor and AMPA receptor function.

The data in table 1 demonstrate that general anaesthetic agents apparently share a common property of inhibiting EAA-mediated neurotransmission at several sites within the mammalian CNS. However, the predominant site and nature of the inhibition differs according to the region of the CNS and the anaesthetic agent under investigation. Presynaptically, this may reflect the variations in $\text{Ca}^{2+}$ channel populations responsible for neurotransmitter release[55] and their different sensitivities to anaesthetics in different areas of the CNS.[76,202] When postsynaptic effects are considered, the recent report that anaesthetic agents can have subunit selective actions at glutamate receptors[50] indicates that variations in *i*Glu-receptor subunit composition throughout the CNS[83] may determine the response to anaesthetics in different brain regions.

## IS INHIBITION OF EAA NEUROTRANSMISSION CAUSAL TO ANAESTHESIA?

If inhibition of EAA-mediated neurotransmission causes the anaesthetic state, then specific pharmacological manipulation of EAA neurotransmission should affect anaesthesia induced by other volatile or i.v. agents. This is clearly seen with glutamate antagonists which markedly reduce the MAC for other anaesthetic agents *in vivo*. This has been demonstrated, for example with the non-competitive NMDA antagonists ketamine,[39] phencyclidine[39,189] and MK-801/dizolcipine[107,189], the competitive NMDA antagonists CGS 19755 and D-CPP-ene[40,107] and agents acting at the polyamine site[41] and also the glycine site[121] of the NMDA receptor. The AMPA receptor competitive antagonist NBQX appears to share similar properties.[120] Furthermore, riluzole (a drug inducing a use-dependent block of presynaptic glutamate fibres[123]) has been reported to reduce the MAC for halothane and potentiate barbiturate anaesthesia *in vivo*.[130]

There is thus convincing evidence that a state of anaesthesia is associated with inhibition of EAA neurotransmission throughout the CNS. Significantly, inhibition of spinal cord EAA neurotransmission[34,186,187] could also contribute to anaesthesia (in the sense of ***unresponsiveness to surgical stimuli***) with the demonstration that the MAC for isoflurane in the rat is independent of forebrain integrity[170,171] and that a site of action distal to the brainstem contributes significantly to the anaesthetic effects of isoflurane in the goat.[4,22]

It must be emphasized that anaesthesia induced in humans with glutamate antagonists such as ketamine or phencyclidine differs from that induced by other anaesthetic agents. It is characterized by sedation, hypertonus, amnesia and profound analgesia[54] and has been termed dissociative anaesthesia, referring to a supposed "dissociation of the limbic from the thalamo-neocortical systems".[35] When auditory evoked responses (AER) are used to assess depth of anaesthesia, it is apparent that the effects of ketamine differ from those of the majority of general anaesthetics. Using this technique, volatile agents, propofol, etomidate and barbiturates significantly reduce the amplitude and increase the latency of the early cortical part of the AER,[94] whereas ketamine (in common with opioids and benzodiazepines) has little or no effect on the AER.[192] Further differences between ketamine and other i.v. anaesthetics are apparent when effects on cerebral metabolism are considered. Barbiturates globally depress cerebral metabolism[80] while other i.v. agents (such as propofol, Althesin and etomidate) predominantly depress forebrain metabolism and spare hindbrain metabolism.[38 42 43] In contrast, anaesthetic doses of ketamine have little effect on metabolism in most brain regions but cause a marked increase in metabolism in the hippocampus.[37 44] Enhanced hippocampal metabolism has also been shown with volatile anaesthetics[146 157] although this is accompanied by global inhibition of metabolism in other brain regions.[77 157]

If the increased hippocampal metabolism seen with anaesthetic doses of ketamine is mediated via its action at the NMDA receptor, then similar increases observed with volatile agents may indicate a common mechanism of action. Conversely, the markedly different effects seen with barbiturates, propofol, etomidate and Althesin suggest that actions on EAA neurotransmission may be less significant with these i.v. anaesthetics. The effects of different anaesthetics on cerebral metabolism may reflect the balance between anaesthetic actions on EAA neurotransmission and inhibitory neurotransmitter systems, notably the $GABA_A$ receptor (for reviews see Frank and Lieb[67] and Pocock and Richards[166]). This balance could in turn determine the clinical manifestations of the anaesthetic state induced by each individual agent.

## EAA and memory: is this how anaesthetics prevent recall?

Sub-anaesthetic or sedative doses of general anaesthetics have powerful inhibitory effects on short term memory,[68 143] and the reduction in the transfer of information from the periphery to the cerebral cortex[3] associated with general anaesthesia prevents the recall of intraoperative events. EAA neurotransmission plays a central role in the pharmacology of learning and memory[90 142]; therefore it is important to consider if this absence of memory for intraoperative events is a consequence of inhibition by general anaesthetics of EAA-mediated processes. In order to do so, it is necessary first to provide an overview of the fundamental mechanisms involved in memory at both synaptic and more global levels, and subsequently to review the available data relating to anaesthetic interactions with these systems.

Current theories propose that at the synaptic level, learning and memory are a consequence of long-term potentiation (LTP) of synapses in specific neuronal pathways within the CNS.[19] First described in the hippocampus by Bliss and Lømo in 1973,[20] LTP is a form of synaptic plasticity causing facilitation of neurotransmission which may last for up to several weeks *in vitro*. LTP has been demonstrated subsequently in other regions of the CNS, including the cerebral cortex[8 17] and spinal cord.[165 172] The mechanisms underlying LTP have been investigated extensively and it is clear that EAA play a key role.

This key role for EAA in memory has been confirmed in animal models of learning using the Morris water maze. This tests the ability of the rat to learn the location of a hidden platform in a tank of opaque water in which it is forced to swim.[142] Intracerebroventricular administration of NMDA antagonists impairs the ability of the rat to learn a new location of the platform but not to find a location that was learned previously; importantly, this impairment is associated with disruption of hippocampal LTP *in vivo*.[142] These and similar data from a variety of animal models of learning and memory provide good evidence that "*NMDA receptors are involved in the acquisition of new information but not in its subsequent retrieval or expression*.[142] Similarly, in humans, administration of sub-anaesthetic doses of the non-competitive NMDA antagonists ketamine and phencyclidine causes dose-dependent anterograde amnesia but has no effect on established memory.[9 69]

The hippocampus undoubtedly plays an important role in learning and memory,[199] as is evident in humans from the gross impairment of short term memory in patients with hippocampal lesions, but it does not function in isolation: current concepts of memory propose that the hippocampus functions in concert with neuronal networks of the cerebral cortex. Memory "traces" are thought to be retained briefly in the cortical areas that process incoming information, but hippocampal activation (presumably involving LTP as described above) is essential to establish *new* memory. After hippocampal activation, medial temporal lobe structures direct the consolidation of memories in specific neuronal networks of the neocortex[198 199] where again NMDA-mediated LTP may play a critical role.[137] Activation of specific hippocampal and cortical regions during learning and memory has been confirmed *in vivo* in humans using positron emission tomography studies of cerebral blood flow[181 210] and has led to the development of a model of hemispheric asymmetry for memory encoding and retrieval (HERA) involving large distributed cortical neuronal networks.[208]

The data discussed above provide a mechanistic model for a human memory system consisting of several systems and subsystems.[219] Two separate systems, explicit memory and implicit memory, can be identified readily by psychological tests. The former requires deliberate and conscious retrieval of information and can be assessed by recall and recognition tests, while the latter does not require conscious recall but is manifest as improvement in performance in skill learning or task-completion tests. General anaesthesia by definition inhibits explicit memory of intraoperative events, however, several studies have demonstrated that some forms of implicit memory may still occur during anaesthesia (reviewed in Ghoneim and Block[68]), thereby suggesting that the different systems of memory may be differentially sensitive to anaesthetics. For example, using sub-anaesthetic concentrations of isoflurane it has been shown that implicit memory occurs at concentrations of isoflurane (0.15–0.3 MAC) that impair explicit recall[57]; and when coherent frequency of auditory evoked response is used to assess quantitatively depth of anaesthesia,[143] inhibition of implicit memory requires a greater depth of anaesthesia than does inhibition of explicit recall.

### DOES INHIBITION OF EAA-DEPENDENT NEUROTRANSMISSION SUPPRESS LEARNING AND MEMORY UNDER GENERAL ANAESTHESIA?

To answer this question we need to consider the mechanisms of hippocampal LTP, the best understood synaptic model of memory.[19] A schematic representation of the processes involved in hippocampal LTP is shown in figure 3.

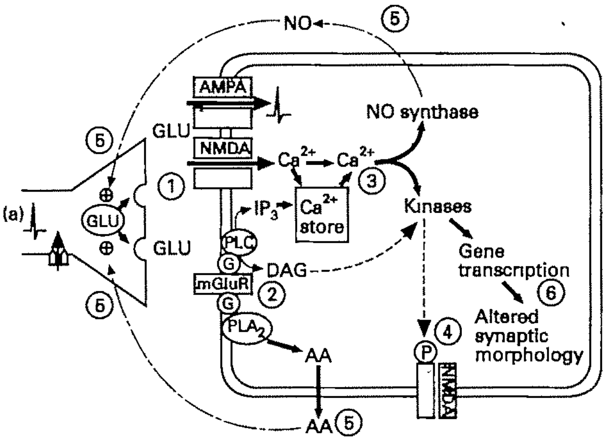

*Figure 3* Schematic representation of the mechanisms involved in hippocampal long-term potentiation (LTP). ① Induction of LTP is dependent on EAA release and NMDA receptor activation resulting in enhanced $Ca^{2+}$ entry into the postsynaptic neurone. ② This $Ca^{2+}$ signal may be supplemented by $Ca^{2+}$ release from inositol 1,4,5-trisphosphate ($IP_3$) gated stores which occurs as a consequence of co-activation of *m*Glu-receptors.[58] ③ The increase in $Ca^{2+}$ concentration in the postsynaptic cell initiates a chain of events at the synapse secondary to the activation of numerous $Ca^{2+}$ dependent enzymes. ④ This results in postsynaptic hyperexcitability as a consequence of phosphorylation and altered expression of membrane proteins, including an increase in EAA receptor number. ⑤ This may be augmented by release of retrograde transmitter(s) (possible candidates include NO and arachidonic acid) causing the presynaptic nerve terminal to enhance its release of EAA. Together pre- and postsynaptic events lead to enhanced transmission at the affected synapses. ⑥ These events are consolidated by changes in gene transcription and altered synaptic morphology, and while *induction* of LTP is prevented by NMDA antagonists, *established* LTP is unaffected by these agents. GLU=Glutamate; NMDA=*N*-methyl-D-aspartate; AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; mGluR=metabotropic glutamate receptor; PIP=phosphatidyl-inositol-4,5-bisphosphate; NO=nitric oxide; PLC=phospholipase C; $IP_3$=inositol-1,4,5-trisphosphate; $IP_3R$=$IP_3$ receptor; $PLA_2$=phospholipase $A_2$; G=GTP-binding protein; P=phosphorylation site; DAG= diacylglycerol; (a)=depolarization and action potential generation.

It is clear that volatile and i.v. anaesthetics inhibit EAA neurotransmission (table 1), and most,[13,101,124,125,126,179] but not all,[161] electrophysiological studies have suggested that hippocampal excitatory neurotransmission in particular is inhibited. Anaesthetic inhibition of EAA release and NMDA receptor function therefore has the potential to modify the induction (step 1) of LTP. Furthermore, there is evidence that $IP_3$-gated $Ca^{2+}$ stores are depleted by volatile anaesthetics[45] suggesting that the second phase of LTP-induction might also be sensitive to volatile anaesthetic inhibition. Is this a means by which anaesthetics suppress learning and memory?

Only two studies have specifically examined the effects of volatile anaesthetics on hippocampal LTP and these have produced conflicting results. MacIver, Tauck and Kendig[126] demonstrated that *in vitro*, both halothane and methoxyflurane at clinically relevant concentrations attenuated excitatory neurotransmission in the hippocampus, but while halothane markedly inhibited induction of LTP, methoxyflurane had no effect. In a separate study in which LTP was induced in the anaesthetized rat *in vivo*, it was reported that hippocampal excitatory neurotransmission and induction of LTP was unaffected by halothane, enflurane or isoflurane at clinically relevant concentrations.[161] The insensitivity of hippocampal neurotransmission to volatile anaesthetics in the latter study does not correlate with the inhibitory effects of volatile anaesthetics reported elsewhere, but it must be noted that control values for hippocampal neurotransmission in this study were measured in animals already anaesthetized with urethane, an agent which may itself affect excitatory neurotransmission in the hippocampus and induction of LTP.[174]

In conclusion, there is clear evidence that inhibition of EAA neurotransmission is a common property of general anaesthetics (although the presynaptic or postsynaptic locus of inhibition may vary with each agent), and direct, or indirect, modification of NMDA receptor function has been putatively proposed as the final common pathway of anaesthetic action.[66] However, although NMDA antagonists both contribute to the anaesthetic state and suppress memory, effects that are clearly associated with inhibition of hippocampal LTP *in vivo*, it remains uncertain if volatile and i.v. anaesthetic agents share this effect on LTP. Further studies are necessary to confirm whether the loss of awareness caused by general anaesthesia is a consequence of inhibition of LTP in the hippocampus or cerebral cortex.

## Excitatory amino acids and pain

Peripheral tissue injury creates a continuing noxious input to the spinal cord via Aδ and C-fibres which results in a progressive increase in the response of neurones within the spinal cord dorsal horn to further afferent input. This plasticity of spinal cord processing of nociceptive information plays a critical role in post-injury pain hypersensitivity[225] and chronic pain syndromes[30] and is termed central

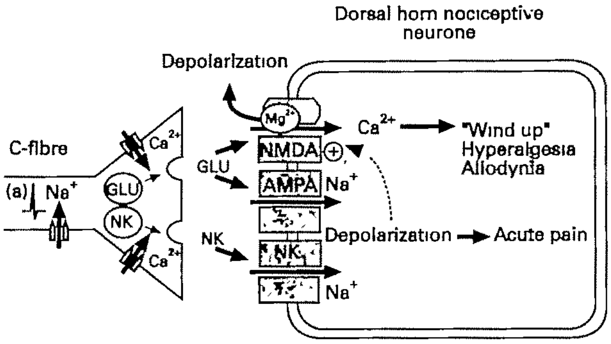

*Figure 4* Diagrammatic representation of the pharmacology of spinal pain transduction within the dorsal horn Acute pain is mediated by glutamate acting at AMPA/KA receptors and neurokinins acting at $NK_1$ receptors, the consequence of which is brief postsynaptic depolarization of dorsal horn neurones and activation of central pain pathways. More prolonged afferent input via Aδ and C-fibres causes NMDA receptor activation when AMPA receptor- and neurokinin receptor-mediated depolarization of the dorsal horn neurone is of sufficient magnitude and duration to remove the $Mg^{2+}$ block of the NMDA receptor LOC. NMDA receptor activation (with possible contribution from *m*Glu-receptor) leads to central sensitization and resultant hyperalgesia. GLU=Glutamate; NMDA=*N*-methyl-D-aspartate; NK=neurokinin; AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; (a)=depolarization and action potential generation.

sensitization. The pharmacology of central sensitization and spinal pain transduction has been a subject of many recent reviews[48 52 212 224 227] and it is clear that EAA play a key role (fig. 4). Aδ and C-fibre primary afferent nerve terminals within the substantia gelatinosa of the spinal cord release glutamate (and neurokinins) in response to noxious stimuli. Glutamate binds to both *i*Glu-receptor and *m*Glu-receptor subtypes which may be co-localized on the same postsynaptic cell. The acute response to injury at the synaptic level is mediated by glutamate acting at AMPA receptors and neurokinins acting at $NK_1$ receptors, the consequence of which is brief depolarization of dorsal horn neurones and activation of central pain pathways. More prolonged afferent input via Aδ and C-fibres causes NMDA receptor activation when AMPA receptor and neurokinin receptor mediated depolarization of the dorsal horn neurone is of sufficient magnitude and duration to remove the $Mg^{2+}$ block of the NMDA receptor channel. NMDA receptor activation (with a possible contribution from *m*Glu-receptor) leads to central sensitization and resultant hyperalgesia. Central sensitization may be consolidated by protein kinase C-mediated phosphorylation of the NMDA receptor which reduces the $Mg^{2+}$ gating characteristics of the channel[26]; indeed, inhibition of protein kinase C has been reported to prevent the development of hyperalgesia in a rat model of central sensitization.[230]

## ANAESTHETIC AND ANALGESIC EFFECTS ON SPINAL EAA MECHANISMS

Before reviewing the analgesic or "anti-hyperalgesic" potential of agents that block EAA receptors, it is of interest to examine how established anaesthetic and analgesic agents may interact with EAA neurotransmission in the spinal cord.

Sub-anaesthetic concentrations of some volatile anaesthetic agents may produce intense analgesia. Trichloroethylene and methoxyflurane were used previously for obstetric analgesia and there is good evidence that isoflurane may be similarly effective.[217] Such analgesia may be a consequence of direct effects on acute pain transduction at the level of the spinal cord where electrophysiological studies have shown isoflurane to inhibit nociceptive responses dependent on both NMDA receptor- and non-NMDA receptor-mediated EAA neurotransmission.[34 186 187] There is also some evidence[1 72 153] that modern volatile anaesthetic agents (halothane, enflurane, isoflurane and desflurane) can partially suppress spinal cord sensitization in a rat model in which subcutaneous formalin injection produces a biphasic behavioural response,[221] the second phase of which corresponds to dorsal horn NMDA receptor activation.[75] However, when formalin-induced sensitization in the spinal cord was measured by expression of the immediate early gene *c-fos* (a molecular marker of nociception[144]) halothane anaesthesia was without effect.[205] Therefore, the potential of volatile anaesthetics to influence pain in the postoperative period may be limited. Nitrous oxide has also been reported to inhibit central sensitization in a dose-dependent manner,[72 153] however nitrous oxide induces endorphin release[65] and its effects on central sensitization are partially reversed by naloxone. This does not suggest a direct effect on spinal EAA neurotransmission, but rather the activation of supraspinal opioid receptor mediated mechanisms which influence spinal sensitization.[70 74] Surprisingly, the effect of combined administration of nitrous oxide with either isoflurane[1] or halothane[72 153] was antagonistic and resulted in markedly less inhibition of central sensitization than did the administration of each volatile agent alone. The mechanism and site of this interaction is unclear, and further studies are warranted to assess the clinical significance of this finding.

The spinal analgesic actions of opioid agonists and $\alpha_2$-receptor agonists, at least in part, involve EAA neurotransmission. The demonstration that inhibition of the release of glutamate from dorsal horn nociceptive neurones is a consequence of both opioid[46 97] and $\alpha_2$-agonist[95] administration may explain their synergistic analgesic effects in animal models of pain.[141 158 159] Postsynaptically the NMDA receptor ion channel complex may be directly modulated in addition by $\mu$ opioid receptor agonists.[184] Furthermore, a complex interrelationship between NMDA receptor and $\mu$-opioid receptor mechanisms may control the development of spinal tolerance and dependence on opioids.[53]

## EAA ANTAGONISTS AS ANALGESICS

There is now a considerable literature encompassing the analgesic or antinociceptive effects of agents that inhibit EAA neurotransmission (for reviews see Dickenson,[48] Dray, Urban and Dickenson,[52] Sukiennik and Kream,[204] Urban, Thompson and Dray[212] and Yaksh and Malmbergh[227]). Many studies have focused on the NMDA receptor, where open-channel blockade,[31,61,228] competitive glutamate antagonism,[31,75] glycine site antagonism[31,49] or polyamine site manipulation[29] modify the response to painful stimuli in animal models of pain. Despite the diversity of pain models that have been used in these and other studies, most data suggest that NMDA receptor antagonism causes significant antinociception against persistent inflammatory or neuropathic models of pain but has little effect on brief nociceptive tests of acute pain. A clear demonstration of this effect is seen with the rat formalin model which may correspond to post-surgical pain; in this model which results in a brief acute pain behavioural response followed after a latent period by a longer inflammatory second phase associated with central sensitization, administration of NMDA receptor antagonists has no effect on the first phase but reduces or abolishes the delayed second phase of this test.[75,228] Similarly, in a study of human experimental pain, ketamine had no effect on a single noxious electrical stimulus, but had a marked analgesic effect on repeated stimuli associated with central sensitization.[6]

Given that the initial response to injury involves activation of AMPA receptors in the substantia gelatinosa, antagonism at this site has the potential to produce analgesia. Two groups have reported that the competitive AMPA antagonist NBQX has antinociceptive effects that differ qualitatively from those of NMDA receptor antagonism,[156,226] but a more recent study[31] failed to demonstrate any antinociceptive effect of AMPA antagonists in a variety of pain models. Irrespective of whether or not AMPA-antagonism can cause analgesia, it should be noted that Dickenson[47] considered that this pharmacological approach might be disadvantageous because it would not target a pathologically activated pain pathway but would inhibit a broad spectrum of afferent and efferent fast excitatory synaptic pathways throughout the CNS. Although NMDA receptor-mediated mechanisms are more specific to pain pathways it is unlikely to be their sole function in the spinal cord, for example spinal NMDA receptor-mediated pathways may also play a key role in the control of locomotion.[2] This could explain the motor dysfunction that has frequently accompanied administration of EAA antagonists and which has important implications regarding the interpretation of their effects in tests of nociception.[31] However, combined administration of competitive and non-competitive NMDA antagonists with agents acting at glycine and polyamine sites can produce highly effective antinociception in the formalin test without behavioural effects or motor dysfunction[32] and suggests that this problem may not be insurmountable.

## Excitatory amino acids and neurotoxicity

After traumatic or ischaemic damage to the CNS there is a pathological release of EAA from neurones and glia which plays a central role in mediating more extensive *excitotoxic* neuronal degeneration. In animal models, massive increases in extracellular levels of glutamate follow ischaemic[12] or traumatic insult to the brain[98] or to the spinal cord.[116] Similar increases in glutamate concentrations have been measured in cerebrospinal fluid in humans after head injury[11] and this increase appears to persist for several days after injury. These increased extracellular glutamate concentrations activate an excitotoxic cascade as a consequence of uncontrolled activation of both *i*Glu-receptors and *m*Glu-receptors. The molecular mechanism of this cascade has been reviewed recently[118] and can be summarized as follows (see fig. 5). $Ca^{2+}$ entry through both EAA-operated and voltage-operated $Ca^{2+}$ channels, together with $Ca^{2+}$ release from intracellular stores results in uncontrolled activation of neuronal protein kinases, phospholipases, proteases and nitric oxide synthase. The consequent proteolysis, lipid peroxidation and free radical formation results in degeneration of central neurones. Although EAA-mediated neuronal death can occur within minutes and a proportion of neurones die in the acute phase of injury, a large number of neurones instead suffer delayed death.[118] Much interest has therefore arisen from the potential to ameliorate excitotoxic neuronal damage by modification of EAA release, EAA receptor antagonism or inhibition of subsequent proteolysis and lipid peroxidation.[122]

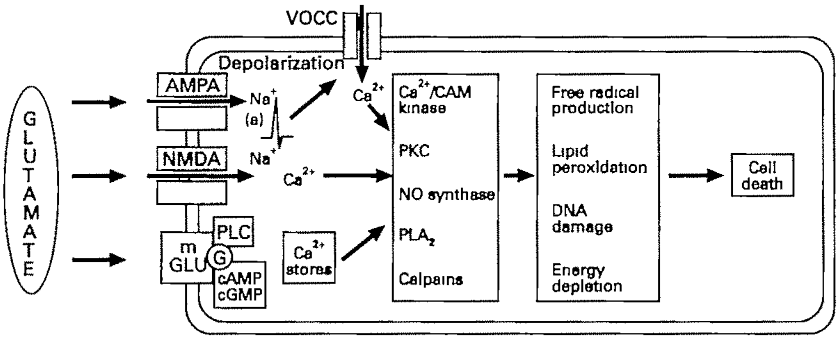

*Figure 5* Schematic representation of the central role of glutamate in excitotoxic neuronal injury (modified and redrawn from Lynch and Dawson[118]). GLU=Glutamate; NMDA=*N*-methyl-D-aspartate; AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; G=G-protein; NO=nitric oxide; PLC=phospholipase C; $PLA_2$ =phospholipase $A_2$; VOCC=voltage-operated $Ca^{2+}$ channel; cAMP=cyclic adenosine 3'-5'-monophosphate; cGMP=cyclic guanine 3'-5'-monophosphate; (a)=depolarization and action potential generation.

### STRATEGIES TO REDUCE EAA RELEASE

Of all the strategies to reduce EAA release, it is essential to first consider the beneficial effects of controlled hypothermia. It is well established that mild to moderate hypothermia results in significant cerebral protection against ischaemic brain injury[214]; this protective effect cannot wholly be explained by a global reduction in cerebral metabolic rate. However, it has recently been reported that mild to moderate hypothermia can markedly reduce the release of glutamate after experimental global cerebral ischaemia.[84] Given that the magnitude of this effect was much greater than the estimated reduction in global cerebral metabolic rate, the authors concluded that a reduction in glutamate release may contribute significantly to the neuroprotective effect of mild to moderate hypothermia.

As discussed previously, volatile anaesthetic agents, notably isoflurane[109] can strongly inhibit the depolarization-evoked release of EAA *in vitro* and it has been argued that this may result in protection from cerebral ischaemia. Recent evidence demonstrates that isoflurane can effectively inhibit the ischaemia-induced release of glutamate to an extent comparable with that of hypothermia[60 147 160] and may also reduce ischaemia-induced NMDA receptor activation *in vitro*,[16] however, in animal models of ischaemic neuronal injury, isoflurane anaesthesia does not appear to reduce injury in comparison with nitrous oxide anaesthesia[215] and its neuroprotective potential *in vivo* remains the subject of debate.

Several novel anticonvulsant agents share a common mechanism of action in that they reduce EAA release from central neurones, probably as a consequence of an inhibitory effect at presynaptic $Na^+$ channels.[211] This class of agents are neuroprotective in animal models of focal or global cerebral ischaemia: thus riluzole,[167] felbamate,[216] lamotrigine and its congeners[196 222] all reduce infarct size or neuronal loss after ischaemic insult and may improve neurological outcome and survival. They are most effective when administered before ischaemia, but importantly, a window of opportunity appears to exist in the immediate post-ischaemic period when their administration is also protective.

### EAA ANTAGONISTS AS NEUROPROTECTIVE AGENTS

Postsynaptic neuronal depolarization, both as a direct consequence of ischaemia and as a result of *i*Glu-receptor activation, removes the $Mg^{2+}$ block of the NMDA receptor thereby allowing uncontrolled $Ca^{2+}$ entry via the NMDA receptor LOC. In consequence NMDA receptor antagonists have attracted much interest as potential cerebral protective agents.[113]

Competitive antagonists at the NMDA receptor such as d-CPP-ene and CGS 19755 are clearly neuroprotective when administered pre-emptively or immediately after injury in models of global and focal ischaemia.[135] However, their efficacy when administered after injury/ischaemia may be limited by the relatively slow penetration into the CNS after parenteral administration, consequently there may therefore be only a narrow window of opportunity for their administration. Open-channel NMDA antagonists such as dizolcipine have the theoretical advantage over competitive EAA antagonists in that antagonism should not be overcome by the pathologically high glutamate concentrations associated with cerebral ischaemia. Dizolcipine clearly provides protection in animal models of cerebral ischaemia[89] and traumatic injury to the brain or spinal cord.[63] Again, cerebral protection is evident whether administered before or after injury, but although agents such as dizolcipine penetrate readily into the CNS after systemic administration, it is unclear if they are more effective when administered after injury than are competitive antagonists. A variety of other open-channel NMDA antagonists have been shown to have experimental neuroprotective properties[113] and, significantly, these include agents which have been used in humans such as the dissociative anaesthetic ketamine[117] and the antitussive agent dextromethorphan.[27 62]

The multiple modulatory sites of the NMDA receptor provide other potential pharmacological targets for cerebral protection. For example, the neuroprotective properties of felbamate may result from glycine site antagonism in addition to its previously described effects on glutamate release.[211 216] Nitroso compounds such as nitroprusside or glyceryl trinitrate which interact with the redox modulatory site and prevent EAA-induced neuronal death *in vitro*,[110 114] are another intriguing class of agents with potential neuroprotective properties.[73] The degree of physiological blockade of the NMDA receptor channel by $Mg^{2+}$ ions may also be an important determinant of neuronal injury, particularly given that tissue $Mg^{2+}$ concentrations have been reported to decline rapidly after both major surgery[185 207] and CNS injury.[111] Magnesium administration has been reported to be protective against CNS ischaemia,[71 195 213] and enhanced blockade of the NMDA receptor channel may at least in part underlie this action.

## Clinical implications

The ubiquity of EAA neurones throughout the CNS emphasizes the importance of EAA-mediated neurotransmission in anaesthesia, analgesia and neurological intensive care. Equally, the importance of EAA neurotransmission in cognition, memory, sensation and motor function certainly contributes to the broad spectrum of neuropsychological side effects that have limited the clinical use of dissociative anaesthetic agents such as ketamine. Nevertheless, we already influence this system with the use of volatile (and to a lesser extent i.v.) anaesthetic agents without all of these adverse effects. Furthermore, there is evidence that indicates that it may be the high affinity of established dissociative anaesthetic agents (including ketamine) for the NMDA receptor, and their slow dissociation from the open-channel binding site, that results in their adverse neuropsychological profile.[180] Drugs with more rapid dissociation kinetics from the open channel, or those interacting with other binding sites on the NMDA receptor, may have a more attractive side effect profile, and these together with their targeting at spinal (as opposed to higher) centres provides the potential for a broader clinical use of these agents. Much interest has centred on the role of EAA neurotransmission in the fields of pain[48 52 212 227] and cerebral protection[89 113 135 180] although less emphasis has been placed on its potential role in anaesthesia.

There is no doubt that inhibition of EAA neurotransmission in the CNS, by antagonism of a variety of receptor sites[39 40 41 120 121 189] and to a lesser extent by inhibition of glutamate release,[130] can promote or induce anaesthesia but the adverse behavioural effects of high doses of many of these agents make it unlikely that they could be widely exploited for clinical anaesthesia, particularly where rapid recovery is required. However, the ability of this group of drugs to reduce the MAC of other anaesthetic agents suggests that they could have a useful role, particularly in high-risk patients. The added advantages of intense analgesia and cerebral protection suggest that inhibition of EAA neurotransmission may contribute to optimally balanced anaesthesia with special relevance to trauma, cardiac and neurosurgery. Furthermore, given the ability of NMDA antagonists to inhibit LTP and induce anterograde amnesia, these agents may prove useful in this high-risk group to reduce the risk of intraoperative awareness.

The importance of the NMDA receptor in the induction and maintenance of central sensitization and the contribution of this process to both acute surgical pain and perhaps more importantly, chronic pain syndromes strongly suggests that agents affecting spinal EAA neurotransmission may be useful analgesic agents in areas where currently available agents are of only limited efficacy. As discussed above, this could involve the systemic administration of such agents as anaesthetic adjuncts, and there is, for example, evidence that systemic peroperative administration of ketamine may reduce postoperative wound hyperalgesia[209] and analgesic requirements[183 209] without psychotomimetic side effects. There is also recent evidence that similar benefit may be achieved with the peroperative administration of magnesium sulphate,[207] an effect that at least in part may be a consequence of NMDA ionophore blockade.

In the chronic pain setting, several reports indicate that ketamine can provide analgesia and relief of hyperaesthesia/allodynia in neuropathic pain resistant to conventional therapy with tricyclic antidepressant, anticonvulsant and membrane stabilizing agents.[10 59 151 200] Similarly, subcutaneous or i.v. infusion of ketamine may be highly efficacious in opioid-resistant cancer pain.[136] Unfortunately, in several cases, dosage has been limited or treatment terminated by psychotomimetic effects, and certainly for outpatient treatment of chronic pain, an agent lacking psychotomimetic effects and suitable for oral administration is ideally required. The antitussive dextromethorphan is the only other agent in clinical use with NMDA antagonist activity[28] and it has a good safety record, but a study of oral administration of this agent failed to show any benefit in a group of patients with neuropathic pain resistant to conventional therapies.[127] However, there is an encouraging recent report of oral administration of ketamine providing pain relief without significant side effects in opioid-resistant neuropathic pain.[23]

In an attempt to limit supraspinally mediated adverse effects, considerable interest has focused on intrathecal or extradural administration of NMDA receptor antagonists, thereby targeting EAA synapses in the substantia gelatinosa of the spinal cord. While experience in human subjects is limited, animal studies convincingly demonstrate the effectiveness of spinally administered NMDA receptor antagonists in a variety of pain models corresponding to both post-surgical and chronic pain states. Although many of the studies of NMDA receptor open-channel blockers such as ketamine and dizolcipine (MK801) have shown significant motor and behavioural effects even after spinal administration, co-administration of low doses of open-channel blockers with agents acting at other regulatory sites on the NMDA receptor may circumvent behavioural and motor problems[32] rendering them more suitable for clinical use. Concern has also been expressed regarding the neurotoxicity of ketamine and dizolcipine.[129 154 155] However, low concentrations of preservative-free ketamine are not neurotoxic[21] and have been used in humans by both intrathecal[18] and extradural[85 99 145 173] routes. Competitive antagonists may have fewer adverse effects and there is evidence that the potent NMDA antagonist CPP is effective in several pain models at doses that do not affect motor function or behaviour.[104] This finding, together with its apparent lack of neurotoxicity[105] or effect on spinal cord blood flow,[103] indicates that CPP may be a prototypical agent for clinical spinal administration in human.

Pathological release of glutamate clearly plays a key role in ischaemic excitotoxic damage to the CNS. It is possible to modify both the release of glutamate and its receptor-mediated effects at multiple sites and a combination of agents acting both pre- and postsynaptically, perhaps in conjunction with mild to moderate hypothermia, may be necessary to minimize neuronal damage. Concern has been expressed over the behavioural and neuropsychological effects of glutamate antagonists—particularly those acting at the NMDA open-channel site—at the dosage required for cerebral protection.[113] However, both memantine (an anti-Parkinsonian drug which blocks the NMDA receptor open-channel site with low affinity and rapid kinetics of dissociation) and felbamate (a glycine site NMDA receptor antagonist and an inhibitor of glutamate release) have been shown to be effective in animal models of CNS ischaemia at concentrations that are tolerated clinically in humans.[25 216] They may therefore be prototypical agents for perioperative use in neurosurgical and perhaps cardiac anaesthesia if rapid recovery is required. The multiple facets of EAA-mediated excitotoxicity provide many intriguing therapeutic possibilities in this area and in addition to evaluating new agents it may be necessary to reappraise the use of established techniques, including volatile anaesthetics, magnesium administration and the use of nitroso compounds such as glyceryl trinitrate.

The clinical pharmacology of EAA neurotransmission is still in its infancy; few of the agents that specifically influence EAA release or interact with the growing family of glutamate receptors have as yet progressed beyond preliminary clinical studies or isolated case reports. Nevertheless, an understanding of this rapidly expanding field of pharmacology is of paramount importance in order that we may optimize our management of high-risk patients and acute or chronic pain.

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SHORT COMMUNICATIONS

# Continuous extradural infusion of ropivacaine 2 mg $ml^{-1}$ for pain relief during labour

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## Summary

We have assessed the dose–response relationship of a solution of ropivacaine 2 mg $ml^{-1}$, given as a continuous extradural infusion to women in labour. A total of 133 parturients were allocated randomly to one of four groups to receive a fixed rate ropivacaine infusion of 4, 6, 8 or 10 ml $h^{-1}$ with additional bolus doses as necessary. Contraction pain, quality of analgesia, sensory block, motor block and neonatal Apgar scores were assessed. There were no significant differences between groups in terms of analgesia or motor block, although significantly more bolus doses were required by the group receiving 4 ml $h^{-1}$ ($P<0.05$ compared with the other groups), and a significantly higher total dose of ropivacaine was administered to the 10-ml $h^{-1}$ group compared with the 6-ml $h^{-1}$ group ($P=0.044$). There were no significant differences between groups in terms of obstetric or neonatal outcome. We conclude that ropivacaine 2 mg $ml^{-1}$ was effective and well tolerated when given as a continuous extradural infusion at 6–8 ml $h^{-1}$ and may be used as the sole analgesic during labour. (*Br. J. Anaesth.* 1997; **78**: 748–750).

**Key words**
Anaesthesia, obstetric. Anaesthetics local, ropivacaine. Analgesia, obstetric. Analgesic techniques, extradural.

Ropivacaine is a long-acting amide local anaesthetic and is the first enantiomerically pure anaesthetic of its type to be developed. It has been shown to have lower central nervous system and cardiovascular toxicity, and to produce slightly less motor block than equivalent doses of bupivacaine in surgical patients.[1] Several studies have compared ropivacaine 2.5 mg $ml^{-1}$ with bupivacaine 2.5 mg $ml^{-1}$ for analgesia in labour.[2–4] Although most factors were found to be affected similarly by each drug, ropivacaine was associated with a significantly lower incidence of instrumental delivery,[3] and higher neurological adaptive capacity scores (NACS) of the neonate, 2 and 24 h after delivery,[3 4] which in one case were significantly improved.[3] Furthermore, a volunteer study[5] suggested that ropivacaine 2 mg $ml^{-1}$ infused at rates of 10, 20 and 30 mg $h^{-1}$, may have a more favourable sensory:motor block ratio than bupivacaine 2.5 mg $ml^{-1}$, given as 25 ml $h^{-1}$. As this lower concentration of ropivacaine has not yet been evaluated in labour, we have investigated the dose–response relationship of different volumes of ropivacaine 2 mg $ml^{-1}$, administered by continuous extradural infusion, in terms of analgesia and motor block during labour, and obstetrical and neonatal outcomes, in a seven-centre open study.

## Methods and results

We studied 134 parturients in whom extradural analgesia was planned, and who were at least 18 yr of age, of less than 110 kg body weight, and pregnant with a singleton fetus (in the vertex position); they were allocated randomly to one of four groups to receive ropivacaine 2 mg $ml^{-1}$ at fixed extradural infusion rates of 4, 6, 8 or 10 ml $h^{-1}$ (8, 12, 16 or 20 mg $h^{-1}$). The investigation, which was approved by the Ethics Committee of the co-ordinating centre, was explained fully to the patients (according to the Helsinki declaration) and written consent was obtained.

Exclusion criteria included: a history of allergy or sensitivity to amide local anaesthetics; administration of analgesics before the extradural; maternal medical conditions such as neurological disease, pre-eclampsia, drug abuse or psychiatric illness; and known fetal abnormalities.

The extradural procedure was started during labour. After local infiltration, a 16–18 gauge Tuohy needle was inserted in one of the L1–4 vertebral

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interspaces and the extradural catheter sited after intravascular or intrathecal placement had been excluded. An initial dose of ropivacaine 10 ml was delivered by fractional injection. The ropivacaine infusion was started within 15 min of the initial dose and was continued until delivery. Additional 5-ml bolus doses were allowed at the discretion of the investigator during the infusion period, providing the total dose did not exceed 450 mg, or 175 mg in any 3-h period.

Administration of oxytocin was allowed at any time during the procedure and patients experiencing hypotension or bradycardia received ephedrine or volume loading, or both. If concurrent analgesics other than nitrous oxide were required before delivery, the patient was withdrawn from the study.

Onset of pain relief was assessed at each contraction using a four-point verbal scale. Contraction pain was assessed using a visual analogue scale (VAS), graded from 0 mm (no pain) to 100 mm (worst imaginable pain). Assessments were made for two consecutive contractions 5–10 min before commencing the extradural procedure, after the initial dosing, and thereafter at the first contraction after successive 30-min intervals. Spread of sensory block was assessed bilaterally every hour by pinprick. Overall quality of pain relief throughout labour was evaluated by the parturient immediately after delivery. Motor block was assessed bilaterally every hour using the modified Bromage scale, and other assessments made are listed in table 1. All adverse events for mother, fetus and neonate were recorded during labour, and at regular post-partum follow-ups until 2–3 weeks after birth. No attempt was made to standardize obstetric management between centres as the primary goal of this study was to evaluate analgesia.

Data were analysed using Wilcoxon rank sum tests or chi-square tests, stratified for centre. *P* values were adjusted for multiple comparisons using the Bonferroni–Holm method and those values <0.05 were considered statistically significant.

The four groups were similar in patient characteristics and 54 women were multiparae. Of the 134 parturients, data from 133 who received ropivacaine were valid for analyses of efficacy and safety and are summarized in table 1.

Duration of treatment, was slightly, but not significantly, longer in the 10-ml h$^{-1}$ group (median 4.63 h compared with 3.55–4.11 h). Total dose of ropivacaine administered, however, was significantly higher in the 10-ml h$^{-1}$ group (median 127.6 mg) than in the 6-ml h$^{-1}$ group (median 84.6 mg). Furthermore, the number of bolus doses administered per hour was significantly higher in the 4-ml h$^{-1}$ group than in the other groups ($P$=0.025 (4 ml h$^{-1}$ *vs* 6 ml h$^{-1}$); $P$=0.001 (4 ml h$^{-1}$ *vs* 8 ml h$^{-1}$); $P$=0.0002 (4 ml h$^{-1}$ *vs* 10 ml h$^{-1}$)). There were no significant differences between groups in any of the characteristics of analgesia and motor block scores immediately before transition to stage 2 of labour. The incidence of spontaneous head delivery was similar between groups (63–76%). Median Apgar scores of all neonates at 1 and 5 min after delivery were 9 and 10, respectively, with four newborns having scores of <7, 1 min after delivery. At 5 min after delivery, only two newborns had scores of <10 and both children registered scores of 9.

The incidence of adverse events was similar between groups. The most frequent adverse event in the mothers, fetuses and neonates was mild to moderate hypotension (19 of 133), deceleration (25 of 133) and temporary jaundice (36 of133), respectively.

*Table 1* Primary efficacy results (median (min–max) or number). *$P$<0.05 compared with 6-ml h$^{-1}$ group; †$P$<0.05 compared with other treatment groups

| | Ropivacaine dose (2 mg ml$^{-1}$ solution) | | | |
|---|---|---|---|---|
| | 4 ml h$^{-1}$ (*n*=34) | 6 ml h$^{-1}$ (*n*=34) | 8 ml h$^{-1}$ (*n*=33) | 10 ml h$^{-1}$ (*n*=32) |
| Total dose (mg) | 86.4 (40–168) | 84.6 (28–218) | 82.8 (10–178) | 127.6 (34–310)* |
| Number of boluses/hour | 1 03 (0.3–4.7)† | 0.65 (0.0–7.2) | 0 40 (0.0–4 9) | 0 41 (0.0–6 0) |
| Duration of treatment (h) | 4.10 (1.2–8.0) | 4.11 (0.7–11.8) | 3.55 (0.1–7.9) | 4 63 (0.4–12 6) |
| Dose rate (mg h$^{-1}$) | 22.4 (15.1–55.9) | 21.8 (14.7–82.5) | 24.6 (18.4–240 0) | 27.8 (21.4–90 9) |
| Onset of pain relief from start of treatment (min) | 16.0 (8–61) | 17.0 (5–45) | 16.0 (1–26) | 16.0 (4–50) |
| VAS scores immediately before delivery | 18.5 (0–100) | 10.0 (0–80) | 20 0 (0–100) | 8.5 (0–100) |
| Quality of pain relief assessed by | | | | |
| The patient (number of patients): | | | | |
| Excellent | 10 | 18 | 14 | 19 |
| Good | 15 | 12 | 14 | 9 |
| Fair | 6 | 1 | 1 | — |
| Poor | 2 | 2 | 2 | 4 |
| None | 1 | 1 | 2 | — |
| Median maximum upper and lower segmental spread of analgesia (median) | T8, S2 | T9, S2 | T8, S2 | T8, S3 |
| Motor block score, on modified Bromage scale, before delivery (number of patients): | | | | |
| Bromage degree 0 | 21 | 18 | 16 | 13 |
| Bromage degree 1 | 8 | 7 | 8 | 12 |
| Bromage degree 2 | 3 | 6 | 3 | 5 |
| Bromage degree 3 | 1 | — | 1 | 1 |
| Time from start of treatment to stage 2 of labour (h) | 3.3 (0.6–10.1) | 3.1 (0.5–10.2) | 3.0 (0.0–7.7) | 3.6 (1.1–9.9) |
| Mode of delivery (number of patients undergoing head delivery · vacuum delivery : Caesarean section: low forceps delivery : high forceps delivery) | 22 : 2 : 1 : 5 : 4 | 22 : 2 : 2 : 2 . 6 | 25 1 : 1 · 3 : 3 | 20 0 : 2 6 : 4 |

## Comment

Ropivacaine 2 mg $ml^{-1}$ was effective as an extradural analgesic. The percentage of patients rating the quality of pain relief as "good" or "excellent" ranged from 74% (4-ml $h^{-1}$ group) to 88% (6- and 10-ml $h^{-1}$ groups). In most patients, VAS scores for subjective pain remained well below the 30-mm score regarded widely as the threshold level at which pain requires treatment. In the group receiving ropivacaine 4 ml $h^{-1}$, median VAS score, however, increased to 30 mm in the last third of labour and significantly more additional bolus doses were required by patients in this group to maintain adequate analgesia throughout labour. The 4-, 6- and 8-ml $h^{-1}$ groups received similar total doses of ropivacaine (median 82.8–86.4 mg) and the 10-ml $h^{-1}$ group received a significantly higher total dose (median 127.6 mg) than the 6-ml $h^{-1}$ group ($P$=0.044). A higher incidence of motor block in the 10-ml $h^{-1}$ group, although potentially troublesome, was not statistically significant.

These findings suggest an optimum infusion rate for ropivacaine 2 mg $ml^{-1}$, of 6–8 ml $h^{-1}$, because at 4 ml $h^{-1}$ more bolus doses per hour were required and there was a trend towards inferior analgesia, while at 10 ml $h^{-1}$ a higher total dose was given and increased motor block detected.

Several studies investigating the use of ropivacaine 2.5 mg $ml^{-1}$ for analgesia in labour have demonstrated that ropivacaine offers advantages over bupivacaine 2.5 mg $ml^{-1}$ in terms of both mode of delivery and neonatal outcome.[2–4] In a prospective meta-analysis[3] in which mean extradural doses of ropivacaine and bupivacaine were 103 (range 12.5–278) mg and 100 (25–337.5) mg, respectively, the number of instrumental deliveries (forceps and vacuum) was significantly less frequent with ropivacaine than with bupivacaine: 27% (54 of 199) *vs* 40% (75 of 188) ($P<0.05$). In addition, the ropivacaine group had significantly better NACS scores 24 h after delivery than the bupivacaine group: 2.8% (four of 144) with a score of less than 35 *vs* 7.6% (11 of 144) ($P<0.05$). There were no differences between the groups in the incidence of adverse events for mothers, fetuses or neonates. It is interesting to note that the dose of ropivacaine administered and the number of instrumental deliveries in our study were both slightly lower than those reported in the meta-analysis.

We conclude that ropivacaine, at a concentration of 2 mg $ml^{-1}$, produced adequate and well-tolerated analgesia for pain in labour when administered as a continuous extradural infusion with supplementary bolus doses. Infusion rates of 6–8 ml $h^{-1}$ are recommended to minimize additional bolus injections and the total dose given.

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# Processed electroencephalogram during combined extradural and general anaesthesia

S. Kiyama and K. Tsuzaki

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## Summary

The processed electroencephalogram (pEEG) was monitored in eight patients undergoing gynaecological laparotomy under combined extradural and nitrous oxide–isoflurane anaesthesia. Pre-incisional mean spectral edge frequency 95 percentile (SEF95) and median frequency (MF) were 11.67 (SD 1.63) Hz and 3.74 (0.24) Hz, respectively. After skin incision, both SEF95 and MF decreased to 6.61 (2.04) Hz and 2.72 (0.32) Hz, respectively ($P<0.001$). An increase in mean arterial pressure after incision suggested inadequate depth of anaesthesia. After introduction of extradural analgesia, these variables returned to pre-incisional values (SEF95 11.65 (1.73); MF 4.02 (0.41)). Reduction of end-tidal isoflurane from 1.0% to 0.5% after extradural analgesia did not cause significant pEEG changes. pEEG may assist anaesthetists to recognize adequacy of combined general–extradural anaesthesia. (*Br. J. Anaesth.* 1997; **78**: 751–753).

**Key words**

Monitoring, electroencephalography. Anaesthetic techniques, extradural. Anaesthetics volatile, isoflurane. Anaesthetics gases, nitrous oxide

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Extradural analgesia has often been combined with light general anaesthesia in major surgery. The sympathetic block produced by extradural analgesia with the negative inotropic action of general anaesthetics may cause further cardiovascular depression. Therefore, it is advisable to avoid a high dose of general anaesthetics in order to prevent haemodynamic derangements.

However, even under adequate extradural analgesia, it is not known if patients remain unconscious during light general anaesthesia. Despite anaesthetists' concerns about intraoperative awareness, particularly in paralysed patients, there have been no studies of intraoperative EEG under combined general–extradural anaesthesia.

## Methods and results

After obtaining Institutional Review Board approval and informed consent, we studied eight ASA I patients, aged 33–66 yr, weighing 45–58 kg, undergoing abdominal hysterectomy.

After oral premedication with ranitidine 150 mg, 2 h before anaesthesia, an extradural catheter was sited at L2–3 or L3–4. Lignocaine 1% (2 ml) was used for local infiltration anaesthesia. Extradural test doses consisted of 3 ml of 1% lignocaine with adrenaline 1:200 000. No further local anaesthetic was given before induction of anaesthesia with thiopentone 5 mg $kg^{-1}$ i.v. Vecuronium was administered to facilitate tracheal intubation and surgical exposure. Positive pressure ventilation was adjusted to maintain normocapnia (end-tidal carbon dioxide partial pressure of 4.5–5.0 kPa), measured with an anaesthetic gas monitor (Capnomac Ultima, Datex, Helsinki, Finland). Non-invasive arterial pressure, electrocardiogram, oxygen saturation, urine output and rectal temperature were monitored.

After induction, the lungs were ventilated with 1.0% end-tidal isoflurane and 65% nitrous oxide in oxygen. We waited 15 min after intubation before the start of surgery (phase 1). During the first 15 min after incision, anaesthesia was continued with the same concentration of inhalation agents as above (phase 2). Then 1.5% plain lignocaine 20 ml were administered extradurally in 5-ml incremental doses in 6 min and inhalation anaesthesia was maintained as above for another 15 min (phase 3). The end-tidal concentration of isoflurane was then reduced to 0.5% with 65% nitrous oxide in oxygen and 15 min elapsed until the end of the study (phase 4).

A Dräger pEEG monitor (Dräger AG, Lübeck, Germany) was used to monitor continuously pEEG. Four disposable electrodes were placed over the frontal and mastoid areas bilaterally. A reference electrode was placed in the frontal midline. Impedance of the electrodes was measured every 3 min and maintained below 5 kΩ throughout the study. Conventional frequency bands were used to describe power spectrum variables. Epoch length of EEG acquisition was 2 s. pEEG data were recorded onto a PC-compatible computer showing the trend of spectral edge frequency (SEF) and raw EEG waveform, and on postoperative replay the trace of raw EEG was inspected to ensure that artefacts caused by diathermy were excluded in the off-line analysis.

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*Table 1* Mean (SD) [95%CI] data of spectral edge frequency 95 percentile (SEF95), median frequency (MF), relative power of each pEEG band and haemodynamic changes. **$P<0.01$ *vs* phase 1, ***<0.001 *vs* phase 1; †††$P<0.001$ *vs* phases 1, 3 and 4

| | Phase 1 (pre-incision) | Phase 2 (pre-extradural) | Phase 3 (extradural/iso = 1.0%) | Phase 4 (extradural/iso = 0.5%) |
|---|---|---|---|---|
| SEF95 (Hz) | 11.67 (1.63)<br>[10.30–13.03] | 6.61 (2.04)†††<br>[4.90–8.32] | 11.65 (1.73)<br>[10.20–13.10] | 12.71 (1.26)<br>[11.65–13.76] |
| MF (Hz) | 3.74 (0.24)<br>[3.53–3.94] | 2.72 (0.32)†††<br>[2.45–2.99] | 4.02 (0.41)<br>[3.67–4.36] | 4.33 (0.50)<br>[3.91–4.75] |
| Beta band (%) | 3.62 (1.85)<br>[2.07–5.16] | 1.12 (0.81)†††<br>[0.44–1.79] | 3.80 (2.35)<br>[1.84–5.76] | 4.95 (1.96)<br>[3.31–6.59] |
| Alpha band (%) | 12.53 (4.18)<br>[9.03–16.03] | 1.23 (0.69)†††<br>[0.65–1.81] | 15.72 (5.02)<br>[11.52–19.92] | 20.31 (4.39)***<br>[16.64–23.98] |
| Theta band (%) | 19.16 (3.04)<br>[16.62–21.70] | 7.37 (1.35)†††<br>[6.24–8.49] | 21.68 (5.10)<br>[17.41–25.95] | 19.00 (3.17)<br>[16.35–21.64] |
| Delta band (%) | 64.69 (3.95)<br>[61.39–68.00] | 90.29 (1.87)†††<br>[88.72–91.86] | 58.80 (5.94)<br>[53.84–63.77] | 55.74 (5.48)**<br>[51.16–60.32] |
| Heart rate (% of baseline) | 107.7 (12.3)<br>[97.4–118.0] | 105.6 (19.8)<br>[89.1–122.1] | 100.4 (18.0)<br>[85.3–115.5] | 99.4 (21.2)<br>[81.6–117.1] |
| Mean arterial pressure (% of baseline) | 89.9 (8.0)<br>[83.2–96.6] | 116.6 (14.8)†††<br>[104.3–129.0] | 79.8 (19.1)<br>[63.8–95.8] | 77.1 (14.2)<br>[65.3–89.0] |

For statistical analysis, the pEEG data were averaged from 10 consecutive epochs in the last 5 min of each study phase. Mean arterial pressure and heart rate were expressed as percentage of baseline values.

One-way repeated measures ANOVA followed by Tukey's multiple comparison was performed using StatView 4.0 (Abacus Concepts, Inc., Berkeley, CA, USA).

There were no differences between the four phases for end-tidal carbon dioxide concentration, oxygen saturation or rectal temperature.

After surgical incision, SEF95 and MF decreased in all eight patients (table 1). After extradural analgesia, these pEEG variables returned to pre-incisional values. There was no significant change in pEEG variables after reduction of end-tidal isoflurane concentration from 1.0% to 0.5%.

The only significant haemodynamic change was an increase in mean arterial pressure after incision.

## Comment

pEEG shifted towards slower waves after incision in all eight patients. Intraoperative EEG slowing has been considered to reflect increased depth of anaesthesia. However, a significant increase in arterial pressure after incision suggests that anaesthesia at that time was not adequate enough to suppress sympathetic responses.

EEG slowing associated with clinical arousal phenomena caused by surgical stimulation is termed "paradoxical arousal".[1] Controversy exists as to the characteristic EEG changes induced by surgery. Sensory stimulation may induce a shift of the dominant EEG frequency towards faster waves,[2 3] which is similar to what occurs during emergence from anaesthesia.[4] On the other hand, Bimar and Bellville described that EEG patterns, as either increases in high-frequency or low-frequency activity, may represent intraoperative arousal.[5] EEG responses with increases in low-frequency activity were most prominent at frontal areas.[6] In our study, electrodes were placed in the bilateral fronto-mastoid areas, thus reflecting mostly electrical activity in the frontal cortex. This may be the reason why "paradoxical arousal" patterns were identified clearly.

All pEEG variables returned to pre-incisional values after extradural analgesia. It may be criticized that it is impossible to assess the efficacy of extradural analgesia in anaesthetized patients. However, with the general–extradural technique, anaesthetists rely on haemodynamic changes to decide on the timing of extradural dosing and assess its effectiveness. Mean arterial pressure decreased significantly after administration of extradural lignocaine. Mean blood loss at that point was less than 50 ml. Therefore, it is likely that the decrease in arterial pressure in phase 3 resulted from effective extradural analgesia. Our results suggest that the "paradoxical arousal" phenomenon disappeared after achievement of analgesia.

Although there was a slight increase in SEF95 after reduction of end-tidal isoflurane from 1.0 to 0.5%, the difference was not statistically significant. Drummond and colleagues identified a threshold value for SEF of 13.6 Hz which provided separation from surgical anaesthesia to pre-arousal state during emergence from isoflurane–nitrous oxide anaesthesia.[4] Mean SEF95 in phase 4 was less than this threshold value and none of our patients had intraoperative recall. In view of the duration of effect of 1.5% lignocaine, it is unlikely that extradural analgesia was wearing off in phases 3 and 4. We assume that when afferent noxious stimuli are interrupted by extradural analgesia, a modest reduction in dose of inhalation agent may not cause significant changes in pEEG variables, although the possibility of low statistical power resulting from small numbers of subjects cannot be excluded.

Cardiovascular variables have been the only variables available to assess the efficacy of extradural analgesia in anaesthetized, paralysed patients. There was a significant change in mean arterial pressure after incision and also after extradural analgesia. It may thus be argued that in these healthy patients, pEEG did not provide any additional information that was not readily apparent from haemodynamic observations. However, intraoperative haemodynamic state can also be affected by other factors apart from depth of anaesthesia, such as volume status and concomitant cardiac medications. Consequently, it may be of clinical significance that pEEG variables showed significant changes after incision and extradural analgesia.

## Acknowledgement

We thank Drager Japan Ltd for loan of the pEEG monitor.

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# "Best" PEEP during one-lung ventilation

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## Summary

Eight patients were studied under general anaesthesia for elective pulmonary lobectomy to see if intrinsic positive end-expired pressure (PEEPi) would appear or increase in the dependent lung during one-lung ventilation (OLV) or if application of external PEEP equal to individually measured PEEPi would produce better arterial oxygenation, haemodynamic state and oxygen delivery than either zero PEEP (ZEEP) or an external PEEP 5 cm $H_2O$ greater than PEEPi. Patients were non-obese, without obstructive airways disease, aged 53–76 yr and ASA <III. They received standardized anaesthesia with fentanyl, 50% nitrous oxide in oxygen and isoflurane; monitoring included radial and fibreoptic pulmonary arterial catheters and intermittent positive pressure ventilation with a tidal volume of 8 ml $kg^{-1}$, 16 bpm, and an I:E ratio of 1:2. PEEPi was measured during two-lung ventilation (TLV) and OLV, using rapid airway occlusion at end-expiration. There was no PEEPi during TLV, but 2–6 mm Hg of PEEPi appeared during OLV. Applying external PEEP equal to individually measured PEEPi reduced venous admixture and increased $Pa_{O_2}$ without a decrease in cardiac index (thus increasing oxygen delivery) compared with ZEEP, but the improvement in pulmonary gas exchange was lost and an additional penalty of reduced cardiac output was imposed when external PEEP was increased to 5 mm Hg above PEEPi. (*Br. J. Anaesth.* 1997; **78**: 754–756).

**Key words**

Surgery, thoracic. Lung, shunting. Ventilation, mechanical. Ventilation, positive end-expiratory pressure. Ventilation, one-lung.

Hypoxaemia during one-lung ventilation (OLV) for thoracotomy in patients in the lateral position remains a clinical problem. In the majority of cases, hypoxaemia can be prevented by the use of a high inspired oxygen concentration ($FI_{O_2}$), by increasing tidal volume or by application of positive end-expiratory pressure (PEEP) to the non-dependent lung. In some clinical situations, however, management of OLV using these techniques is inappropriate or ineffective for maintaining adequate oxygenation.

Accordingly, the use of PEEP to the ventilated, dependent lung[1,2] is used to minimize ($PA_{O_2}-Pa_{O_2}$) and improve oxygenation during OLV in the lateral position. However, use of excessive PEEP to the dependent lung often impairs oxygenation by diverting blood to the non-dependent lung. Contradictory results have been reported in previous studies on the use of PEEP to the dependent lung during OLV.[1,2] Hence, it is important to devise anaesthetic techniques which provide optimal arterial oxygenation during OLV.

Under most circumstances, airway resistance increases because of a decrease in the compliance of the dependent lung during OLV with the patient in the lateral position, while intrinsic PEEP (PEEPi) is most likely to exist when airway resistance is increased.[3,4] In this regard, PEEPi is likely to appear in the dependent lung during OLV in the patient in the lateral decubitus position, primarily because of high airway resistance from a relatively small tracheal tube at the minute volumes and ventilatory frequencies used during OLV. Moreover, PEEPi, which is used in several types of mechanical ventilation, is suggested to improve oxygenation, and we hypothesized that each patient has an individual optimal PEEP which could be close to measured PEEPi.

Based on these considerations, this study was conducted in patients with normal pulmonary function to exclude any effects of obstructive airways disease on production of PEEPi, to clarify if PEEPi would appear in the dependent lung during OLV in patients in the lateral position, and to determine the PEEP value that best enhanced both oxygenation and haemodynamic state when zero PEEP (ZEEP), the equivalent PEEPi value or PEEPi plus 5 mm Hg was randomly applied externally to the dependent lung during OLV.

## Methods and results

We studied eight adult patients, ASA I or II, aged 53–76 yr, undergoing mechanical ventilation via a double lumen endobronchial tube for elective lung lobectomy. The study was approved by our Clinical Investigation Committee, and informed consent was obtained from each patient. No patient was obese and none had a history of obstructive airways disease.

After arrival in the operating room, an i.v. cannula

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and a radial arterial catheter were placed for infusion of lactated Ringer's solution 5 ml $kg^{-1}$ $h^{-1}$ and for continuous monitoring of arterial pressure and arterial blood sampling, respectively. General anaesthesia was induced with thiamylal 5 mg $kg^{-1}$ i.v. and the left main bronchus was intubated orally after vecuronium 0.2 mg $kg^{-1}$ i.v. Anaesthesia was maintained with 1% inspired isoflurane and nitrous oxide in oxygen ($FI_{O_2}$=0.5), delivered via a left-sided 37-Fr double lumen tube (Broncho-cath; Mallinckrodt Laboratories Co., Ltd., Athlone, Ireland), in addition to a total i.v. dose of fentanyl 5 μg $kg^{-1}$. The lungs were ventilated mechanically throughout the study with a tidal volume of 8 ml $kg^{-1}$, ventilatory frequency of 16 bpm and an inspiratory to expiratory ratio of 1:2. A 7.5-Fr pulmonary artery catheter (oximetry/right ventricular ejection fraction (RVEF) thermodilution catheter, model 93A-750H-7.5F, Baxter, Irvine, CA, USA) was inserted and advanced into the pulmonary artery. Haemodynamic and oxygenation data were obtained from the radial artery catheter and the pulmonary artery catheter.

## MEASUREMENT OF PEEPI VALUE

Airway pressure, including PEEPi, was measured via a side hole proximal to the endobronchial tube using a calibrated pressure transducer. We used the rapid airway occlusion technique to detect and measure PEEPi at end-tidal expiration during TLV with the patient in the supine and lateral positions, and during OLV with the patient in the supine and lateral positions.

After a stabilization period of 20 min, measurements were made during conventional TLV in the supine position. Next, after patients were placed in the lateral decubitus position, the same measurements were performed during TLV. After right or left thoracotomy, measurements were repeated during OLV with external application of ZEEP, PEEP equivalent to PEEPi in each patient, and PEEPi plus 5 mm Hg to the dependent lung. All measurements were carried out after patients were judged to have reached a steady state by confirming stability of $Sp_{O_2}$, arterial pressure, heart rate and airway pressure for at least 10 min. Measurements during OLV with external application of ZEEP, PEEPi and PEEPi plus 5 mm Hg to the dependent lung were performed randomly, and were completed within 60 min before manipulation of the pulmonary vessels. CI, $\dot{Q}s/\dot{Q}t$, $Do_2I$ and pulmonary vascular resistance index (PVRI) were calculated using standard formulae.

## STATISTICAL ANALYSIS

All values are expressed as mean (SD). Statistical comparisons were performed using ANOVA for repeated measures with Fisher's least significant difference test for *post hoc* analysis. $P<0.05$ was considered the minimum level of statistical significance.

We found that a PEEPi of 4 (2) mm Hg (range 2–6 mm Hg) appeared in the dependent lung during OLV in the lateral position. In contrast, PEEPi did not appear during TLV in the supine and lateral decubitus positions. In addition, PEEPi did not appear during OLV in the supine position. PEEPi of 5–6 mm Hg was noted in patient Nos 3, 5, 6 and 7 in whom peak airway pressure increased by more than 7 mm Hg during OLV compared with that during TLV. Haemoglobin concentration remained unchanged throughout the study.

When ZEEP was applied to the dependent lung during OLV in the lateral position, $Pa_{O_2}$, $\dot{Q}s/\dot{Q}t$, CI, $Do_2I$, RVEF and PVRI were 12.3 (3.3) kPa, 30 (11) %, 3.14 (0.74) litre $min^{-1}$ $m^{-2}$, 500 (153) ml $min^{-1}$ $m^{-2}$, 33 (5) % and 208 (64) dyn s $cm^{-5}$ $m^{-2}$, respectively (fig. 1). External application of PEEPi

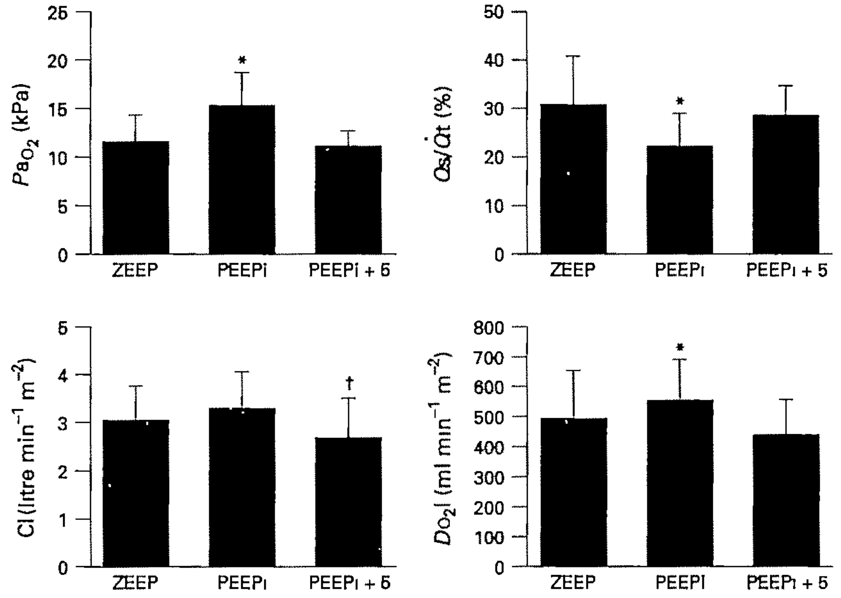

*Figure 1* Changes in arterial partial pressure of oxygen ($Pa_{O_2}$), physiological shunt ($\dot{Q}s/\dot{Q}t$), cardiac index (CI) and oxygen delivery index ($Do_2I$) during one-lung ventilation with external application of zero end-expiratory pressure (ZEEP), intrinsic PEEP (PEEPi) and PEEPi plus 5 mm Hg (PEEPi +5) to the dependent lung, while patients were placed in the lateral decubitus position $^*P<0.05$ compared with other two periods; $^†P<0.05$ compared with the period of PEEPi application.

observed in each patient to the dependent lung significantly increased $Pa_{O_2}$ to 16.0 (4.0) kPa, $Do_2I$ to 552 (144) ml $min^{-1}$ $m^{-2}$ and RVEF to 38 (8) % ($P<0.05$), and significantly decreased $\dot{Q}s/\dot{Q}t$ to 23 (7) % ($P<0.05$), without altering CI (3.39 (0.81) litre $min^{-1}$ $m^{-2}$) or PVRI (220 (58) dyn s $cm^{-5}$ $m^{-2}$).

In contrast, compared with values during application of PEEPi, external application of PEEPi plus 5 mm Hg to the dependent lung during OLV increased $\dot{Q}s/\dot{Q}t$ to 28 (6) % and PVRI to 286 (109) dyn s $cm^{-5}$ $m^{-2}$ ($P<0.05$) and decreased $Pa_{O_2}$ to 11.5 (1.7) kPa, CI to 2.75 (0.86) litre $min^{-1}$ $m^{-2}$, $Do_2I$ to 436 (120) ml $min^{-1}$ $m^{-2}$ and RVEF to 33 (9) % ($P<0.05$). As a result, this intervention restored $Pa_{O_2}$, $Do_2I$, $\dot{Q}s/\dot{Q}t$ and RVEF towards values during OLV with application of ZEEP to the dependent lung (fig. 1), but decreased CI and increased PVRI compared with values during application of ZEEP or PEEPi ($P<0.05$).

## Comment

PEEPi is most likely to exist when airway resistance is increased or when pulmonary gas trapping or pulmonary hyperinflation occurs.[3 4] We anticipated that PEEPi could appear in the dependent lung during OLV primarily because of high airway resistance from a relatively small endobronchial tube and we demonstrated in this study that this occurred in patients with normal pulmonary function. Blood flow to the non-dependent lung is reduced during OLV in the lateral position by force of gravity, surgical compression and hypoxic pulmonary vasoconstriction.[5] Although the precise mechanism(s) for the development of PEEPi during OLV in the lateral position has not been fully elucidated, it seems likely that the development of PEEPi during OLV was caused by the high resistance of the single lumen through which one lung was allowed to empty, slowing expiratory airflow, resulting in incomplete emptying of the lung during expiration. Furthermore, based on our findings that patients with higher PEEPi showed a greater increase in airway pressure, we cannot exclude the possibility that increased blood flow to the dependent lung during OLV compressed peripheral airways, causing further air trapping in alveolar spaces. In addition, end-expiratory occlusion pressures would reflect increased closing pressures in the dependent lung as a result of reduced elastic recoil from downward displacement of the mediastinum.

Manoeuvres recommended to prevent hypoxaemia during OLV include the use of a high inspired oxygen concentration, increased tidal volume, PEEP to the non-dependent lung[1] or dependent lung PEEP.[1 2] However, the beneficial effect of PEEP during OLV remains controversial; some workers found that oxygenation was improved,[5] unchanged[2] or decreased.[1] These divergent results may be explained, at least partly, by the assumption that each patient has her or his own PEEPi value, and the existence of an optimal PEEP for the dependent lung PEEP for each patient is suggested by our results. The most accepted mechanism by which application of external PEEP is thought to be beneficial is that it causes an increase in lung volume at end-expiration (functional residual capacity (FRC)).[5] The increase in FRC contributes to the prevention of airway and alveolar closure at end-expiration. The increase in lung volume and alveolar opening results in increases in lung compliance and the ventilation–perfusion ratio of the ventilated dependent lung. However, if PEEP-induced intra-alveolar vessel compression is widespread because of excessive PEEP, total pulmonary vascular resistance increases and cardiac output decreases.[5] Consequently, intrapulmonary shunt increases and $Pa_{O_2}$ decreases because of diversion of blood flow away from the ventilated dependent lung to the non-ventilated non-dependent lung.[5]

As the minimal PEEP value was reported to be "better PEEP",[6] it seems appropriate to administer the least amount of PEEP necessary to maintain an adequate $Pa_{O_2}$ at a non-toxic $FI_{O_2}$. In this regard, and also for the purpose of maintaining high CI and RVEF, we recommend using a PEEP value equal to the measured PEEPi value. However, we cannot comment on the effects of PEEP values less than PEEPi applied to the dependent lung on oxygenation and haemodynamic state during OLV in the lateral position, as this issue was not examined in the our study. Despite this limitation, because the therapeutic margin of using PEEP to the ventilated dependent lung to increase $Pa_{O_2}$ during OLV is narrow,[5] we suggest that an optimal PEEP value should be close to that actually measured (PEEPi). However, one should be cautious before applying our results to patients with obstructive airways disease.

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# Antioxidant potential of i.v. fluids

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## Summary

In acute clinical settings where there may be a role for antioxidant therapy, patients receive large amounts of i.v. fluids which may have antioxidant activity. To investigate such effects the antioxidant capacity of nine i.v. fluids was measured (Gelofusine, Haemaccel, 20% mannitol, 4.5% human albumin solution, fresh frozen plasma, aprotinin, *N*-acetylcysteine and two hydroxyethyl starch solutions). Results are expressed as mean mmol litre$^{-1}$ Trolox equivalents. Mannitol 20% and the hydroxyethyl starch solutions had no antioxidant activity. Protein-containing solutions (gelatins, albumin and aprotinin) had antioxidant activity 50–66% that of plasma: Gelofusine 0.85 mmol litre$^{-1}$; Haemaccel 0.78 mmol litre$^{-1}$; 4.5% albumin 0.95 mmol litre$^{-1}$; aprotinin 0.80 mmol litre$^{-1}$; fresh frozen plasma 1.45 mmol litre$^{-1}$. However, none was nearly as potent an antioxidant as the clinical preparation of *N*-acetylcysteine, with an antioxidant activity of 502 mmol litre$^{-1}$. Studies of antioxidant therapy may need to take account of the antioxidant effect of i.v. fluids. (*Br. J. Anaesth.* 1997; **78**: 757–759).

**Key words**
Fluids, i.v.

In critical care settings such as septic shock[1] and during or after the reperfusion injury that occurs with, for example, liver transplantation[2] or cardiopulmonary bypass[3], plasma concentrations of antioxidants have been found to decrease. At the same time, there is evidence of increased oxidant-induced cell damage. This has led to the hypothesis that free radical species (in particular the reactive oxygen species) may play an important pathogenic role in local and systemic inflammatory responses. It follows that antioxidants may have a therapeutic role in such clinical settings. In addition to specific antioxidants, it is likely that these groups of patients receive considerable amounts of i.v. fluids. The chemical nature of these solutions suggests that they themselves may be antioxidants. Some are protein or peptide solutions with amino acid side chains which would be expected to have antioxidant activity.[4] Others are starches with multiple hydroxyl groups which may have potential antioxidant activity.[5]

## Methods and results

The antioxidant capacity of nine fluids was measured using the method described by Miller and colleagues.[4] In brief, this assay relies on conversion of a phenothiazine 2,2-azinobis-(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) to a long-lived radical cation (ABTS$^{\bullet +}$) by hydrogen peroxide in the presence of metmyoglobin acting as a peroxidase. ABTS$^{\bullet +}$ was produced in a linear manner and the concentration measured by spectrophotometry 10 min after initiation of the reaction. Addition of antioxidants to the assay delays the production of ABTS$^{\bullet +}$ so that there is apparent inhibition of oxidation compared with saline controls. A standard curve was constructed using the water-soluble vitamin E analogue Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid). All reagents were obtained from Sigma (UK), except Trolox which was obtained from Aldrich (UK). Metmyoglobin was purified as described by Miller and colleagues to give a final purity of >90% total haem protein.

A standard curve was plotted as percentage inhibition of ABTS$^{\bullet +}$ formation when Trolox 0.5, 1.0, 1.5, 2.0 and 2.5 mmol litre$^{-1}$ was present compared with controls without Trolox. Ten measurements were made for each point and the mean was used to plot the standard curve. There was an SD of 7% about each point, indicating a precision similar to that in the original description of the method.[4]

The total antioxidant capacity of any fluid (or dilution of it) added in place of Trolox to the assay can be expressed as mmol litre$^{-1}$ Trolox equivalent activity. The fluids studied were Gelofusine (Braun), Haemaccel (Hoerst), 20% mannitol (Baxter), 4.5% human albumin solution (Bio Products Laboratory), fresh frozen plasma (National Blood Transfusion Service), aprotinin (Bayer), *N*-acetylcysteine (Evans) and two 6% hydroxyethyl starch solutions (Dupont and Laevosan).

The antioxidant capacity of each fluid was measured neat except for *N*-acetylcysteine (formulation concentration 200 mg ml$^{-1}$). This was diluted

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*Table 1* Mean (SD) antioxidant capacity of nine i.v. fluids

| Fluid | Mean Trolox equivalent (mmol/litre$^{-1}$) |
|---|---|
| Gelofusine | 0.85 (0.12) |
| Haemaccel | 0.78 (0.14) |
| 20% Mannitol | 0 (0.19) |
| 4.5% Human albumin | 0.95 (0.08) |
| Fresh frozen plasma | 1.45 (0.10) |
| Hespan—Dupont | 0 (0 21) |
| Hespan—Laevosan | 0 (0.22) |
| Aprotinin—Trasylol | 0.80 (0.07) |
| N-acetylcysteine | 502 (14) |

to the recommended initial therapeutic concentration of 150 mg kg$^{-1}$ in 200 ml for a 70-kg patient as this is the fluid normally infused. In fact, this solution was so potent that it had to be diluted a further 200-fold with phosphate-buffered saline to fall within the Trolox reference range.

The antioxidant capacity of each fluid was measured 10 times and the results, which appeared to have a normal distribution, expressed as mean (SD). The statistical package used was StatView 4.1 Power PC version for Apple Macintosh computers (Abacus Concepts, Inc).

The results of these experiments are shown in table 1. All protein-containing fluids (gelatins, 4.5% albumin, plasma and aprotinin) had antioxidant activity. The hydroxyethyl starch and mannitol solutions had no antioxidant activity. As would be expected, *N*-acetylcysteine had potent antioxidant activity in this system. The 200-fold dilution had an antioxidant capacity of 2.51 (0.07) mmol litre$^{-1}$, an equivalent of 502 mmol litre$^{-1}$ for the solution used clinically. When the relative concentrations are accounted for, *N*-acetylcysteine 1 mmol litre$^{-1}$ had antioxidant activity equivalent to Trolox 1.56 mmol litre$^{-1}$.

## Comment

The finding that all the protein solutions have antioxidant activity is to be expected. This is because proteins have amino acid constituents with antioxidant activity such as sulphydryl, hydroxyl and carboxyl groups. In the article by Miller and colleagues describing the method used here, evidence was presented that albumin is the largest single contributor to total plasma antioxidant capacity.[4] It has an antioxidant potency equivalent to Trolox and a high plasma concentration compared with other antioxidants, which make up the difference between the measured albumin and total plasma antioxidant capacities. In this study, measurements of total plasma antioxidant capacity, represented by fresh frozen plasma, of 1.45 mmol litre$^{-1}$ agreed with those of Miller and colleagues whose mean value was 1.46 mmol litre$^{-1}$ with a similar degree of variation. This suggests a comparable performance of this assay in our laboratory to the original report.

It is perhaps surprising that the gelatin solutions, Gelofusine and Haemaccel, were nearly as potent as the 4.5% albumin solution. Gelatin consists largely of polyglycine which, because it has only the simplest amino acid side chain (-H) would not be expected to have antioxidant activity. It may be that gelatin modification by succinyl- (Gelofusine) or urea- (Haemaccel) linkage might increase the antioxidant activity. Both urea and succinate, a dicarboxylate, are antioxidants. The similar antioxidant potentials of the gelatin solutions and 4.5% albumin cannot be explained in terms of a higher protein concentration in the gelatin solutions as Gelofusine is a 4% solution and Haemaccel a 3.5% solution.

In common with the gelatin solutions, the clinical formulation of aprotinin has an antioxidant potential which approaches that of 4.5% albumin solution. This may be an additional attraction when used for its antifibrinolytic action during cardiopulmonary bypass.

The finding that the hydroxyethyl starch solutions had no antioxidant activity was not surprising, as starches are relatively inert compared with proteins. Starches do have hydroxyl (-OH) groups which can have antioxidant activity. However, in polyhydroxy compounds, such as starch, they are much less reactive than in monohydroxy compounds[5] which include some potent antioxidants.

Mannitol had no activity in either our experiments or those of Miller and colleagues.[4] In many articles mannitol is claimed to be a potent hydroxyl radical scavenger. If this is so, then it may not be an antioxidant in this particular system where the following reactions are thought to occur:

$$\mathrm{HX\text{-}MbFe^{3+} + H_2O_2 \rightarrow {}^{\bullet}X\text{-}Mb^{4+}\text{-}OH + H_2O}$$

$$\mathrm{2\,{}^{\bullet}X\text{-}Mb^{4+}\text{-}OH + 2ABTS \rightarrow 2HX\text{-}MbFe^{3+} + 2ABTS^{\bullet +} + O_2}$$

Hydrogen peroxide ($H_2O_2$) oxidizes metmyoglobin ($HX\text{-}MbFe^{3+}$) to form ferrylmyoglobin (${}^{\bullet}X\text{-}Mb^{4+}\text{-}OH$), a highly reactive bi-radical, which oxidizes ABTS to its stable radical cation ($ABTS^{\bullet +}$) with regeneration of metmyoglobin. No hydroxyl radicals are formed in this system and therefore a pure hydroxyl radical scavenger would not inhibit these reactions. However, in experiments such as those of Del Maestro and colleagues[6] which are cited widely by authors referring to mannitol as a potent hydroxyl radical scavenger, a mixture of reactive oxygen species was present. Therefore, it is not clear that mannitol is a pure hydroxyl scavenger. There are two explanations for what was observed: either mannitol is not an effective antioxidant (indeed some work from the organic chemistry literature suggests that polyhydroxy compounds such as mannitol would not be potent antioxidants)[5] or that mannitol scavenges reactive oxygen species, but the radical produced is itself highly reactive and contributes to oxidant stress. Whatever the explanation, this must cast doubt on the potential usefulness of mannitol as a therapeutic antioxidant.

As expected, the most potent antioxidant solution was *N*-acetylcysteine which is probably the best available agent to investigate for any therapeutic role. However, being water soluble, it may not be the best agent to protect lipid membranes which are highly susceptible to oxidant-induced injury.

In summary, except for *N*-acetylcysteine, all i.v. fluids investigated had no or only modest antioxidant activity. They are therefore probably of little therapeutic use. However, in clinical studies describing a small antioxidant effect of any therapy, investigators may need to be aware of a possible confounding effect of protein-containing i.v. fluids.

## Acknowledgements

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CASE REPORT

# Perioperative use of the oesophageal Doppler probe (ODM II) on a patient scheduled for transmyocardial revascularization

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## Summary

We describe the use of the continuous wave oesophageal Doppler monitor (ODM II) in the perioperative management of a patient with chronic obstructive coronary artery disease undergoing transmyocardial revascularization (TMR). The use of ODM II allowed both quantitative and qualitative assessment of cardiac function relatively non-invasively. It detected the successful transmyocardial penetration of a laser beam during operation by visual and auditory phenomena in addition to reflecting improvement in cardiac performance after operation. (*Br. J. Anaesth.* 1997; **78**: 760–761).

**Key words**
Measurement techniques, Doppler echocardiography. Complications, coronary artery disease. Surgery, cardiovascular.

Transmyocardial revascularization (TMR) is a new surgical technique that is used in patients with chronic obstructive coronary artery disease that is refractory to conventional revascularization techniques and to maximal medical therapy. In this group of patients with end-stage coronary artery disease the chosen anaesthetic technique should minimize the haemodynamic changes imposed in the perioperative period and be tailored to meet the requirements of the procedure. Perioperative monitoring should provide early detection of haemodynamic changes and indicate the successful transmyocardial penetration of a laser beam during operation. We describe the successful and informative use of the continuous wave oesophageal Doppler (ODM II) in a patient undergoing TMR. The ODM II provides a visual display of the spectral analysis of the Doppler frequency shifts back-scattered from blood flow in the descending thoracic aorta allowing non-invasive assessment of cardiac output, which is provided by minute distance, the product of waveform area (stroke distance) and heart rate.[1] In addition, the device allows indirect assessment of left ventricular filling, contractility and resistance to ejection.[2]

## Case report

A 60-yr-old, 75-kg male, ASA class IV, who had two consecutive coronary artery bypass grafting (CABG) operations but continued to suffer from limiting angina regardless of full medical therapy was offered TMR. After overnight sedation with lorazepam 4 mg he received morphine 10 mg and hyoscine 0.3 mg as premedication. The right radial artery and left forearm peripheral vein were cannulated with 20-gauge and 14-gauge cannulae, respectively, under local anaesthetic. Anaesthesia was induced with propofol 100 mg (as an infusion over 3 min) and alfentanil 1.5 mg. After neuromuscular block with atracurium 50 mg, an ODM II Doppler probe was placed in the oesophagus and a large left-sided Robertshaw double lumen tube was positioned and the lungs ventilated with an air–oxygen mixture. Baseline cardiac index was 2.5 litre $m^{-2}$ $min^{-1}$. A central vein was cannulated via the right internal jugular vein using a triple lumen catheter. An extradural catheter was then sited at the mid-thoracic level (T6–7) and pain relief was produced with an infusion of 0.125% bupivacaine and fentanyl 5 $\mu g\ ml^{-1}$ at a rate of 5 ml $h^{-1}$ via the extradural catheter after an initial bolus dose of 7 ml of the solution before surgery. Anaesthesia and neuromuscular block were maintained with propofol 3 mg $kg^{-1}$ $h^{-1}$ and atracurium 0.5 mg $kg^{-1}$ $h^{-1}$ infusions, respectively. Standard monitoring was used, including $F_{I_{O_2}}$, ECG, pulse oximetry, direct arterial and central venous pressures, and ventilatory variables.

After a left anterior thoracotomy, one lung ventilation was commenced and the heart was exposed. Holes were drilled through the ischaemic myocardium by the laser beam and confirmed by the ODM II with visual (showers of ultrasound echoes) and auditory "whoosh" phenomena. A total of 22 holes were made. The patient tolerated the procedure well and his trachea was extubated immediately after surgery. He was then transferred to the intensive care unit. The patient was monitored closely in the postoperative period and remained haemodynamically stable with adequate gas exchange. The extradural infusion was continued for 24 h. He was pain free and felt subjectively improved. The Doppler probe was left *in situ* for 8 h after operation

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and cardiac index was recorded continuously for that period. Cardiac index remained increased from baseline and varied from 3.9 to 4.5 litre $m^{-2} min^{-1}$. The probe was removed after 8 h as the patient started taking fluids.

## Discussion

It has been shown that producing small holes in the ischaemic myocardium by a laser beam improves functional status and offers a ray of hope for these sick patients.[3] During operation, which is performed on the beating heart through a left thoracotomy, a high energy laser is used to bore transmural channels into the left ventricle so that blood flows directly from the left ventricle into the channels and then into the myocardial vascular plexus.[4] Restoring perfusion should alleviate ischaemia in a potentially viable myocardium and improve ventricular function. Postoperative thallium stress tests and left ventriculography indicate that the channels remain patent and protect the ischaemic muscle. There has been anatomical evidence of patent endothelialized channels which contained red blood cells suggesting that the laser channels were functional.[5]

A trans-oesophageal echocardiography (TOE) probe has been used in the past. It requires an additional medical person trained in TOE, it is not tolerated by an awake patient after operation and is costly. We suggest that the use of a continuous wave oesophageal Doppler probe can prove very useful in the intraoperative detection of flow turbulence during successful puncture and assessment of cardiac function in the immediate postoperative period. It is much smaller in size and tolerated better than a TOE probe by an awake patient after operation. The probe is positioned in the lower third of the oesophagus. An indication of which is the "best" signal can be assessed from the one with the highest peak velocity (PV). The ultrasound beam is reflected from the red blood cells travelling in the aorta and the resultant change in frequency is picked up by the probe and relayed to the monitor which calculates the velocity of blood in the descending aorta and from this calculates stroke volume, cardiac output and other associated variables in real time and for each heart beat. There is a signal quality bar which allows determination of whether the quality of the signal has changed as the probe was positioned. The correct signal has a very clear systolic pulse with a very low or totally absent diastolic flow. There is potential for movement artefact when the quality of the signal changes, for example if the patient's position is changed it is possible to pick up a signal from venous and intracardiac sources, but these are easily recognized and corrected. The spectral waveform gives an indication of linear movement of blood in the aorta. To change these data from linear into volumetric, the computer uses a conversion table based on the age, sex and mean arterial pressure of the patient to produce a volume conversion factor (K) for that patient. This is multiplied by minute distance (MD) which is acquired from multiplying heart rate and stroke distance (distance moved by a column of blood for one cardiac cycle). This is used to produce continuous cardiac output (CO) data ($CO = MD \times K$ in litre $min^{-1}$). It was noted that cardiac index doubled and sometimes tripled immediately after successful penetration for approximately 1 min.

Animal data suggest that TMR is an alternative method of treating ischaemic heart disease in terms of both short- and long-term improvement in myocardial contractility and also for the diminished area at risk from necrosis.[6] The optimum number of transmural channels per area, spacing and placement of channels, and contribution of the channel to overall perfusion still need to be quantified. Although it is too early to draw any conclusions it may be that the creation of transmyocardial channels increases cardiac index by improving the inotropic function of the myocardium in the immediate postoperative period. Previous studies have shown that estimation of cardiac output can be made to approximately 90% accuracy with a considerably lower coefficient of variation[7] compared with a standard thermodilution method.

As TMR is taking its place in the treatment of patients with chronic obstructive coronary artery disease, we believe that the use of the ODM II in the perioperative period is a simple, reliable and useful guide for detection of successful penetration of an ischaemic myocardium. It is a good guide for measurement of cardiac output in the perioperative period and is minimally invasive providing flow-based rather than pressure-based monitoring.[8]

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COMMENTARIES

# Toward the paperless hospital?

R. H. R. HARPER, K. P. A. O'HARA, A. J. SELLEN AND D. J. R. DUTHIE

**Summary**

This report describes an ethnographic study of document use by anaesthetists. In doing so, it focuses on the role of the preoperative risk assessment form as used in anaesthetic practice at a cardiothoracic hospital, and considers what would be the advantages and disadvantages of shifting the paper into the electronic form. Evidence from this case study is used to comment on how the practical use of documents by medical professionals can be fundamentally at odds with how the organization at large would like to use them. We argue that hospital trusts need to take into account this practical perspective in order to build effective, on-line document systems. (*Br. J. Anaesth.* 1997; **78**: 762–767).

**Key words**
Records, anaesthesia. Records, anaesthesia, computerized. Computers. Anaesthesia, audit. Anaesthetists, activity.

Hospitals, in common with most other organizations, depend on a wide range of documents for the day-to-day accomplishment of work. These documents take on a myriad of formats, both paper-based and computer-based. With advances in digital technologies, there are many pressures to do away with what is often perceived to be the unnecessary clutter and cost of paper documents. There is a common perception that improved efficiency and productivity can be gained by transferring information "on-line" to take advantage of computer-based tools.

We report on a study of anaesthetic practice, the purpose of which was to understand the practical aspects of document use in a medical organization, and the implications of paper documents moving "on-line". The method reported is based on "sociological ethnography", a branch of sociology which developed from a social anthropological tradition that involved "ethnographers" spending long periods of time closely observing small scale societies. This approach has been developed for the observation of social behaviour within any and all institutions. It involves observation of work and activities in their "natural" setting, in addition to extensive interviewing. As such, it offers an "outsider's" perspective on anaesthetic practice and document use.[1]

For this case study, we chose to focus on anaesthetists because the research team already had some background knowledge and experience in studying anaesthetic practice.[2–4] The hospital which we selected for the study is a cardiothoracic hospital where there is a desire to take advantage of new technology in developing its document practices.

While we considered all of the key documents that anaesthetists in this hospital use, we were concerned mainly with the *preoperative risk assessment (PRA) form* which was designed within the study hospital. Although not every hospital trust uses such a form or even ones that are similar, we focused on this form because it contains the most extensive set of anaesthetic relevant data and, as such, is seen as potentially a useful resource for organizational purposes such as auditing and assessing preoperative risk. Indeed, one of the general purposes of the PRA form when it was first introduced was that it would contain data which would be useful for audit purposes and risk stratification. The information contained in the forms could then be used to calculate various statistical scores, such as UK ACTA (UK Association of Cardiothoracic Anaesthetists) and Parsonnet.[5]

However, this hospital has experienced two major obstacles to using the data in this way. First, the PRA forms tend to be filled out inadequately, making analysis difficult. Second, the data are in paper form and therefore need to be entered manually into the electronic system. Currently, the paper forms are sent to a central store in theatre reception so that the data can be entered later into a computer. However, for the most part, the paper remains in store and no major effort, to date, has been made to use the data.

The PRA form therefore represents an interesting case of a document which, while now well established in use in this particular hospital, is seen to fall short in terms of serving its original purposes. As it happened, it was also a particularly opportune time to conduct the study as a new electronic alternative to the paper PRA form was about to be introduced.

Although this is a study of the use of one particular type of form in one hospital, we believe that findings from this study can be applied to medical document systems at large. The case of the PRA form illustrates how the practical use of documents

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by medical practitioners can sometimes be fundamentally at odds with organizational aims and purposes. We discuss the reasons why, and argue that these practical issues need to be taken into account in order for medical document systems to effectively move forward.

## Methods

There are a variety of ways that document-related activities can be investigated. For example, one standard procedure is to conduct a time and motion study of document use. However, this type of technique overlooks the motivations that underlie people's activities, and the particular perspective that professionals take toward their work. One technique that can capture these concerns is sociological ethnography. This approach involves close observation of work as it occurs *in situ* and extensive open-ended interviews.

In this study, the ethnographic approach was used to understand the ways in which anaesthetists responded to the particular circumstances in which they found themselves, and the practical concerns that they brought to their work. Throughout, the focus was on how documents—and the PRA form in particular—played a role in this work. The study took place over a period of 5 days. Specifically, this ethnographic approach involved:

(1) Observing anaesthetists at all stages of their work, from patient interviews to the operating theatre to the recovery unit.

(2) Examining what was done with the PRA form during its entire life cycle. This began at the point where anaesthetists were observed going through patients' files at the ward reception, and ended with observing their postoperative use.

(3) Undertaking interviews with trainees and consultants about their work. When possible, these interviews focused on particular examples of PRA forms which were in the process of being completed.

These activities generated a detailed picture of the work in question, and in particular the practical, "real world" orientation of anaesthetists.

## Results

The ethnography found that, from the anaesthetist's perspective, the PRA form had a significant role within two main stages of the work: during the interview with the patient and in the anaesthetic room.

The patient interview stage, normally undertaken on the day before an operation, can be characterized as an information gathering stage with the PRA form serving as an information repository. Most of the information to be entered on the form is prespecified, but some is also added in the form of free-hand notes. While information is also obtained from the patient's notes at this stage, much of it can be gathered only from the patient during the interview (for example NYHA status, dentition and drug allergies).

In its role as an information repository, the PRA form serves three main purposes. The first is to enable the anaesthetist to think about and plan the anaesthetic during the operation on the following day. The second is to enable the anaesthetist to write notes to serve as reminders during the impending operation. (Such reminders are especially important given that anaesthetists may manage several anaesthetics during a list.) The third purpose is to enable the "handing over" of an operation to another anaesthetist should the need arise. Because of the volumes of work and the fact that the workload cannot always be predicted, it is not always possible to ensure that the person who interviews a patient is also the one managing the operation.

During the second phase—in the anaesthetic room—the PRA form is used mainly as a reference source before induction of anaesthesia. It is here that free-hand, written reminders can be critical to the smooth management of the anaesthetic, and it is here that a colleague's notes taken during the patient interview serve their purpose.

For the anaesthetist, when anaesthesia is induced, the PRA form remains available but has effectively come to the end of its useful life. In terms of documents in the operating theatre, the anaesthetist turns his or her attention primarily to completing the anaesthetic record. It is unlikely that the anaesthetist will look at the PRA form again, although sometimes the surgeons or other operating theatre staff may do so.

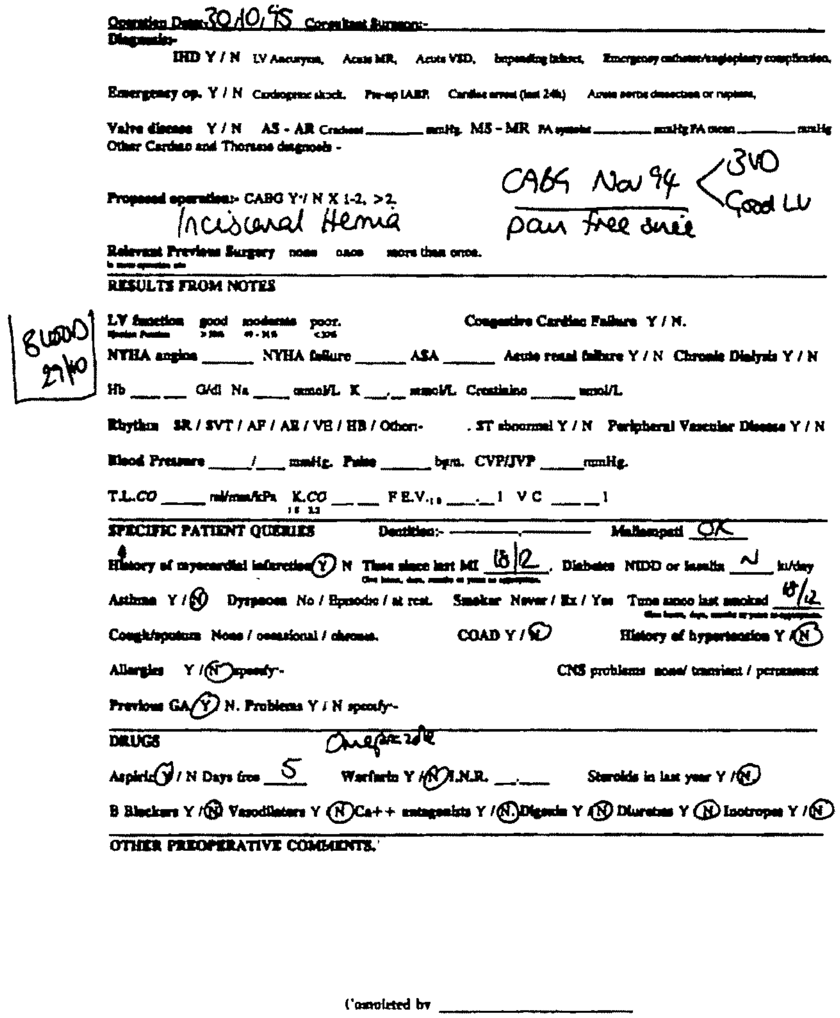
This description helps to make clear the practical role of the PRA form. For these anaesthetists, the PRA form serves as a unitary repository of information and reference tool. As such, our observations confirmed that this paper document is not only adequate, but is a useful practical tool in facilitating anaesthetic work.

However, our observations also confirmed that, for organizational purposes (i.e. data for computing UK ACTA scores or for carrying out organizational audits), there are two ways in which the forms are inadequate or problematic: the data on the forms are incomplete and there are difficulties in transforming the paper-based data into electronic data.

### PROBLEM OF INCOMPLETE DATA

If the information on the PRA form is examined in detail, it is apparent that there are almost always missing data. Indeed, of the 517 PRA forms we had at our disposal, none contained complete information. We also found that most consultants never filled out a PRA form. Of the three consultants we observed that did so, two filled out only 10 of the 517 forms. We learned that most consultants prefer to delegate this job to trainee staff. Consultants still use the forms to manage operations, but they use their junior colleagues' PRA forms. A by-product of this is that the consultants' practice is in part undocumented and it is only the trainees whose assessments are recorded.

We believe that the salient issue here is not who fills out the form but the relationship between documents and how they are used. Why are the data so incomplete? One reason often cited by hospital trust managers, systems designers and other commentators on hospital life is that anaesthetists (in



Operation Date: 30/10/95 Consultant Surgeon:-

Diagnosis:-

IHD Y / N LV Aneurysm, Acute MR, Acute VSD, Impending Infarct, Emergency catheter/angioplasty complication,

Emergency op. Y / N Cardiogenic shock, Pre-op IABP, Cardiac arrest (last 24h) Acute aortic dissection or rupture,

Valve disease Y / N AS - AR Gradient ______ mmHg, MS - MR PA systolic ______ mmHg PA mean ______ mmHg

Other Cardiac and Thoracic diagnosis -

CABG Nov 94 < 3VD Good LV

pain free since

Proposed operation:- CABG Y / N X 1-2, >2.

Incisional Hernia

Relevant Previous Surgery none once more than once.

RESULTS FROM NOTES

BLOOD 27/10

LV function good moderate poor.  Congestive Cardiac Failure Y / N.

NYHA angina ______ NYHA failure ______ ASA ______ Acute renal failure Y / N Chronic Dialysis Y / N

Hb ______ G/dl Na ______ mmol/L K ___.___ mmol/L Creatinine ______ umol/L

Rhythm SR / SVT / AF / AE / VE / HB / Other- . ST abnormal Y / N Peripheral Vascular Disease Y / N

Blood Pressure ______/______ mmHg. Pulse ______ bpm. CVP/JVP ______ mmHg.

T.L.CO ______ ml/min/kPa K.CO ___ ___ F.E.V.1.0 ___.___ l V C ______ l

SPECIFIC PATIENT QUERIES Dentition:- ______ Mallampati OK

History of myocardial infarction [✓ Y] N Time since last MI 18/12. Diabetes NIDD or insulin ~ iu/day

Asthma Y / [✓ N] Dyspnoea No / Episodic / at rest. Smoker Never / Ex / Yes Time since last smoked 18/12

Cough/sputum None / occasional / chronic. COAD Y / [✓ N] History of hypertension Y / [✓ N]

Allergies Y / [✓ N] specify- CNS problems none / transient / permanent

Previous GA [✓ Y] N. Problems Y / N specify-

DRUGS Omeprazole

Aspirin [✓ Y] / N Days free 5 Warfarin Y / [✓ N] I.N.R. ___.___ Steroids in last year Y / [✓ N]

B Blockers Y / [✓ N] Vasodilators Y / [✓ N] Ca++ antagonists Y / [✓ N] Digoxin Y / [✓ N] Diuretics Y / [✓ N] Inotropes Y / [✓ N]

OTHER PREOPERATIVE COMMENTS.

Completed by ______________

*Figure 1* Example of a preoperative risk assessment (PRA) form.

common with any group of professionals) are simply unwilling to fill out forms correctly. We believe, however, that this is to misunderstand the issues. On closer inspection of the PRA forms and the associated work practices, there are at least two good reasons why PRA forms show absence of information. The first is related to the fact that anaesthetists adapt the PRA form in such a way as to transform a form designed for *general purposes* into one that is useful for *specific purposes.* In other words, anaesthetists treat the PRA form as a device that enables them to gather information that they need for that particular operation, and not as a device for the gathering of information for generalized use—whether it be for *post hoc* analysis or administrative audit. By way of example, a copy of a real form is shown in figure 1, altered only in order to disguise the identities of the patient and anaesthetist. Most of the fields in the section labelled *Diagnosis*, are blank; all the fields under the section *Results from Notes* have not been completed.

The reason for the lack of data is the fact that in *this* case, for *this* operation and for *this* patient, the information requested in those sections was not as relevant. This patient was about to have an operation on an incisional hernia. Previous cardiac surgery had provided symptomatic benefit and there had been no subsequent cardiac catheterization. For these reasons, the anaesthetist made the judgement that, from his point of view, it was not worth the effort of entering the information on the form.

This does not mean that the form was of no use. This example shows that what is omitted may be as informative as what is completed. In this example, the anaesthetist has written in the operation being undertaken. Concerns which were relevant for this operation were then remarked upon, in this case in the section marked *Specific Patient Queries.* Therefore, questions on allergies, history of hypertension, and so on, were answered. Thus, if another anaesthetist needed to refer to this form, they would be able to know the areas of concern by seeing what operation was scheduled. In this respect, the form is filled out *correctly*, that is providing information that anaesthetists need in the course of their work.

One could argue that the form in figure 1 is simply inappropriate for this particular operation, or that this is an exceptional case. However, we found that this case exemplifies, although perhaps exaggerates, how all PRA forms are used.

The second, perhaps more mundane, reason for incomplete data is that, in some situations, the information anaesthetists require is not available. Patients' notes are often so extensive that it makes information difficult, if not impossible, to find. Different wards often have their own ways of organizing a patient's file and the patient's previous hospital may have different standards of record keeping. This too can make it difficult to find facts. Often the cost in time and effort of prolonged searches for information may not justify the small benefits to be obtained from certain types of information (e.g. height).

Further, some information, although ideally important for the anaesthetists, may not be available when the form is filled out. An example of this type of information is blood test data: haemoglobin counts are very useful to anaesthetists but may not be available when they undertake the patient interview.

Taken as a whole, these considerations could indicate that there are good reasons for PRA forms to be somewhat bad clinical records—bad in the sense that they are never filled out completely (cf. quality of records in mental health agencies).[6] However, to think of them in this way is to ignore the fact that these forms are useful for anaesthetists in that they record local knowledge and needs, and reflect the requirements of each particular case.

### USE OF PAPER

The second major obstacle to organizational use is that the PRA data are paper-based and need to be entered manually into the computer system. Our observations confirmed that, in the face of many other more pressing demands, the rather tedious job of entering this information into the system was not a high priority. Consequently the data were not transferred.

What might be the impact of replacing the paper PRA system with a computer-based PRA system? In order to assess this, we first need to consider in more detail the ways in which the paper form serves important functions in the various phases of anaesthetists' work. There were three main advantages to the use of paper that we observed.

#### *(1) Flexibility of paper*

We have already seen that the task of filling out the PRA form through consultation of patients' notes may result in omitting information either because it is not always important to a specific case or because it is not always available. Because it is a paper form, this allows a flexibility of completeness whereby only the relevant information for that particular patient is recorded. Free text annotation is also easy with paper and thus short explanatory notes and reminders can be added to the form. This type of information cannot be expressed easily within the constraints of a structured on-line form. The paper form is thus highly flexible.

#### *(2) Non-disruptive nature of paper*

Related to the flexibility issue is the fact that paper is a medium that supports non-intrusive ways of taking notes during a patient interview because it can be marked directly in a relatively unconstrained way (cf. the process of general practitioner–patient interviews).[7] Thus note taking can be interweaved easily with the ongoing discussion. This is important because the patient interview is not simply about obtaining information from the patient. It can often be a delicate social activity which is there to help make the patient feel more comfortable about the nature of the operation and to personalize the situation for both the patient and anaesthetist. At present, paper supports this process because it allows attention to be devoted to the management of the interview.

#### *(3) Portability of paper*

A third set of issues relates to the fact that paper is portable and that its contents are quickly accessible. These properties are important in all stages of the life of the PRA form. It is important during preparation of the PRA form in conjunction with the patient's notes because it is sometimes the case that the forms are filled out away from the busy ward rooms. At the bedside, the portability and accessibility of the paper PRA form is important in supporting the patient interview process. With paper, anaesthetists can make use of a clipboard resting on their knees. Portability is also beneficial between operations: sometimes the anaesthetist may consult the PRA form while moving between different operating theatres in preparation for a new patient.

## Discussion

### IMPLICATIONS FOR MOVING ON-LINE

From this case study, we have seen that the PRA form is an example of a medical document which is tailored in accordance with the practical realities and idiosyncrasies of each case. As a result, this often implies that data are missing and forms are incomplete. We have also discussed the ways in which the fact that the paper PRA is flexible, non-disruptive and portable can make it a very useful device in support of the work practices of medical professionals. Both facts militate against efforts to aggregate the data on-line and use it for statistical analysis.

Yet there are many potential benefits to moving to an electronic PRA system. As we have already discussed, from the Trust's point of view, there are the benefits of the reduced cost of storage space, and of using a format that allows aggregation of data and on-line analysis. With regard to the problem of incompleteness, a technological alternative could force anaesthetists to be more complete by requiring them to fill out every field, and by preventing them from bypassing fields until data are entered.

This is not to say that electronic document systems need necessarily always work to the benefit of Hospital Trusts and to the detriment of medical professionals. Electronic access to data may be very advantageous to practitioners in the course of preparing and referring to a medical form. It may help to eliminate much of the redundant form-filling activity that currently occurs with paper forms by linking to a centralized data store. It may solve problems of accessing and retrieving data that are otherwise difficult to find among paper notes, or which are generated by different departments or hospitals. It can help in ensuring that data are as up-to-date as possible. It could also provide remote access to information. At the present time, some consultants obtain information read to them over the phone by trainees. The introduction of digital technologies could offer networked access to the forms. This would have at least two advantages: first, it would release trainees from making phone calls to their superiors; second, it would allow consultants to access information when and where they need it (e.g. from home or from another hospital).

However, designing such systems is challenging. We have discussed the importance of the flexibility, markability, portability and accessibility of the paper PRA form. Most current electronic document systems tend to provide more structured and constrained interfaces, require indirect forms of input via keyboards, are relatively immobile and are cumbersome to navigate. Added to this are problems of screen size, viewing angle and the ability to share multiple documents concurrently by people in the same room.

The new electronic system now in place in the hospital we studied suffers from many of these problems. Perhaps unsurprisingly, therefore, the paper PRA form continues to be used throughout its "natural life cycle" from the ward room to the operating theatre for all the reasons that we have outlined. Anaesthetists then enter the data from the paper PRA forms into the new electronic system, usually during the course of an operation. This means that the paper PRA form continues to be the useful artefact for the anaesthetist. Entering the information electronically simply resuscitates the document after its "organizational death". The new system therefore does not directly support the day-to-day activities of the anaesthetists, but is an additional activity that is required purely for purposes outside the local concerns of the practitioner. The success of the system therefore relies primarily on a "moral obligation" on the part of the anaesthetists to complete the form, rather than on good clinical reasons to do so.

The question, then, is whether one can devise electronic document systems that concurrently serve the purposes of *both* the medical practitioner and the organization at large. Such a technology would have to be suited for all stages of the life cycle of the PRA form. For the first stage, the patient interview, the device would have to allow ease of navigation, incompleteness of data entry and free text entry. One way of providing these features is to offer a relatively unconstrained interface; another is to allow more direct input via electronic stylus devices, for example.

The electronic alternative to the paper PRA form must also have the flexibility to be used not just at the bedside, but in the ward rooms, in the anaesthetic room, in the operating theatre or even moving between theatres. It must not be affected by the constraints imposed by these environments. For example, at the patient's bedside there are no desks or supporting surfaces. This may make even lightweight portable computers cumbersome to use. Other considerations include poor lighting conditions, which suggests the need for good displays which are legible at a range viewing angles.

Finally, in the anaesthetic room and the operating theatre the technology must not hinder staff accessing various documents concurrently. Therefore, a technological solution which provides only one display screen for access to the PRA form and other documents may be problematic (although this could be managed by users "taking turns" for screen access).

For all of these reasons, we believe an effective technological alternative to the paper-based PRA form requires careful design and iterative testing in a real work setting. These requirements also suggest that the best design options will rely on new technologies that are currently still in their developmental infancy (e.g. portable, wireless computing, pen input and lightweight, high resolution screen technologies). In the meantime, an alternative approach is to accept the fact that paper is a tool that is extremely useful for some types of medical documentation including the PRA form, at least in the foreseeable future. This approach involves: (1) distinguishing between those types of medical documents which are best kept as paper and those which are best transferred to the digital realm; (2) concentrating on technologies which bridge the paper and electronic world, such as scanners; and (3) investigating and developing further those technologies and techniques that bring further "intelligence" to these scanning technologies through the use of such procedures as bar coding to facilitate document identification and tracking.

With regard to (2) and (3), this implies viewing such technologies not simply as a way of dealing with the legacy of paper, but rather as a way of supporting an ongoing mix of paper and electronic media.

Any of the above approaches requires a comprehensive understanding of the work practices of medical professionals in relation to the documents they use. In particular, they require an understanding of how practical requirements of medical practice can lead to the use of documentation that is not ideally suited for generalized consumption and use. Changes can be brought about in these practices with the introduction of new technologies, but must not be at the expense of the requirements of clinical professionals. In this article, we hope to have demonstrated one approach which is capable of uncovering what those practical concerns may be, and their implications for the design of new document technologies. Further use of this approach will, we suggest, lead to decisions about investment in electronic or in mixed paper and electronic document systems that are based on more accurate appraisals of the balance between the local, practical needs of medical professionals and those generalized needs of NHS Trusts as a whole.

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# Guidelines for autologous transfusion. II. Perioperative haemodilution and cell salvage

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## 1. Introduction

Part I of the Guidelines for Autologous Transfusion dealt with preoperative autologous donation and was published by the British Committee for Standards in Haematology (BCSH) Task Force in 1993.[1] Part II deals with acute normovolaemic haemodilution in the perioperative period and red cell salvage procedures.

The purpose of all forms of autologous transfusion is to avoid the transfusion of allogeneic blood. This may be necessitated, for instance, by difficulty in obtaining compatible blood for a particular patient, for example when the patient has a rare blood group or when multiple red cell antibodies are present, but more commonly is used as a general strategy for avoidance of the risks (infectious and immunological) of allogeneic transfusion. Autologous transfusion procedures are not usually acceptable to Jehovah's Witnesses, although some accept intraoperative cell salvage (see below). The option must be discussed with patients individually.

In order to maximize the potential benefits, the various forms of autologous transfusion should be seen as complementary, and it is essential that an appropriate transfusion strategy should be developed for each individual patient's needs. Co-ordination of autologous transfusion procedures is of vital importance, with clear methods for communicating whether pre-deposited autologous blood is available as it may be unnecessary to use additional autologous techniques in some patients. It must be remembered that the serious risks of allogeneic transfusion are lower in the UK than in many other countries, and that the procedures used for autologous transfusion of whatever type must be considered carefully so as to minimize potential adverse effects of the procedure itself. The decision to transfuse the autologous blood should be based on that particular patient's need for blood, rather than simply on its availability.

Specific consent for autologous transfusion procedures carried out in theatre is not considered to be necessary. Currently this requirement is considered to be covered by generic surgical consent, although patients must be given full information about the proposed treatment. The information sheet should state that it may be necessary to administer allogeneic blood in an emergency.

While these guidelines seek to deal with situations likely to be met in current clinical practice it is recognized that exceptional circumstances may arise and that the final decision regarding the use of autologous transfusion rests with the consultant (or deputy) who undertakes the procedure.

## 2. Acute normovolaemic haemodilution

1. Acute normovolaemic haemodilution (ANH) is defined as the removal of blood from a patient immediately before operation, either before or shortly after induction of anaesthesia, and simultaneous replacement with an appropriate volume of crystalloid or colloid fluids, alone or in combination, such as to maintain the circulating volume.

The risks of haemodilution (i.e. of a low intraoperative haematocrit) can be minimized by limiting its extent (target haematocrit 25–30%); however, studies using mathematical modelling techniques suggest that savings in allogeneic blood use in such circumstances are likely to be small. Prospective controlled studies are needed to elucidate the effectiveness or otherwise of moderate ANH in reducing the need for allogeneic transfusion.[2]

Extreme haemodilution (target haematocrit <20%) is likely to be more efficacious in reducing allogeneic transfusion requirements, but the risks are correspondingly greater. This procedure should be restricted to relatively healthy patients with a low risk

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of ischaemic heart disease and must be supervised by an expert anaesthetist using appropriate monitoring techniques.

A degree of haemodilution is inevitable in patients on cardiopulmonary bypass unless a blood prime is used; this must be taken into account when additional haemodilution is undertaken.

2. Preoperative apheresis to obtain autologous platelets/FFP/red cells should currently be viewed as a research technique, the benefits of which are not proved. These techniques cannot yet be considered to have a place in routine practice.

3. ANH may confer benefits other than those implied by the avoidance of allogeneic transfusion, for example reduction in red cell loss during operation (secondary to reduced haematocrit) and improved oxygen delivery (secondary to reduction in whole blood viscosity). The availability of blood containing normal concentrations of coagulation factors and functioning platelets for transfusion at the end of the procedure is of theoretical benefit. There is no evidence that these factors confer measurable clinical benefit.

4. The decision to recommend ANH for an individual patient should lie with the anaesthetist and surgeon. The responsibility for the procedure itself normally lies with the anaesthetist. The involvement of the haematologist in charge of the blood bank is to be encouraged, both in developing transfusion strategies and in assisting with the production of standard operating procedures. Where appropriate the consultants in the local transfusion centre should be invited to assist in the training of staff and the production of SOPs.

## 5. SELECTION OF PATIENTS

ANH should only be considered when the potential blood loss is likely to be greater than 20% of blood volume. ANH should not be considered unless the preoperative haemoglobin concentration is $>110$ g litre$^{-1}$. Although the risk of complications relating to unsuspected atheromatous disease, particularly silent myocardial ischaemia, increases with age, patients of any age may be considered for the procedure. Particular caution should be exercised in patients more than 45 yr of age in the assessment of the risk of underlying ischaemic heart disease, and in patients with severe diseases of other systems.

Patients with severe myocardial disease of any cause, for example moderate to severe left ventricular impairment, unstable angina, severe aortic stenosis, critical left main stem disease or the equivalent, should only undergo haemodilution over and above that necessarily incurred during cardiopulmonary bypass with extreme caution.

6. Patients undergoing ANH need not be screened routinely for viral markers. Universal precautions to protect staff from the risks of virus transmission must always be observed. The used container and giving set must be disposed of in accordance with the hospital policy for the disposal of hazardous waste; the fate of all units must be documented.

## 7. PROCEDURES

A suggested operating procedure is outlined in appendix 1.

The safety of ANH depends on the maintenance of normovolaemia. In all patients, care must be taken to match the continuous replacement of volume with the removal of blood. In older patients and where cardiac disease may be suspected, additional care is necessary.

Appropriate blood collection packs must be used to ensure a standard anticoagulant/blood ratio. The approximate volume of blood to be removed (in litres) to achieve the desired haematocrit can be calculated using the following formula:

$$V = \mathrm{EBV} \times (\mathrm{H}_0 - \mathrm{H}_f \,/\, \mathrm{H}_{av})$$

where $V$=volume to be removed, EBV=estimated blood volume (usually taken as 70 ml/kg body weight), $\mathrm{H}_0$=initial haematocrit, $\mathrm{H}_f$=desired haematocrit and $\mathrm{H}_{av}$=average haematocrit (mean of $\mathrm{H}_0$ and $\mathrm{H}_f$).

8. (i) *Labelling.* All units must be labelled with the patient's name, hospital number, date of birth, date and time of collection, and the name of the person carrying out the procedure. The label must be clear, and should state "UNTESTED BLOOD: FOR AUTOLOGOUS USE ONLY". Pre-infusion checks of identity are mandatory and should be equivalent to the hospital's standard procedures for administration of allogeneic blood.

(ii) *Storage.* Blood removed during haemodilution must remain with the patient and should not be removed to a blood fridge. It may be kept for up to 6 h at room temperature, preferably in an insulated box or other container to minimize temperature fluctuations. The container should be labelled with the patient's full details with a warning that it must not be used for another patient.

(iii) *Disposal.* In general all such blood should be used in theatre. If ANH blood is transported with the patient to a recovery area or ward, a written procedure should be in place to ensure that the blood is handled and administered to the patient according to the standards outlined in (i) and (ii) above. Blood from patients known to have markers for viral infections (HIV, HBV, HCV) must not be allowed to leave theatre unless the infusion has already commenced.

Any unused autologous blood is to be disposed of as hazardous waste, preferably in theatre; the fate of all units must be documented. These procedures should be included in a local standard operating procedure which should also include instructions to ensure that no autologous blood is transferred to the general blood supply.

9. The number of units of blood and total volume removed from the patient must be recorded in the patient's case notes. Where allogeneic blood is given, the reasons must be documented clearly in the patient's notes.

10. Serious adverse events should be reported to the hospital transfusion committee and to any appropriate national reporting system.

11. Regular audit of procedures should be undertaken under the aegis of the hospital transfusion committee. Audit and comparison with allogeneic blood usage would be facilitated by the routine recording of autologous blood use in theatre.

## 3. **Red cell salvage**

1. The indications, contraindications, potential adverse effects and range of methods of red cell salvage are described in appendix 2.

2. A designated member of the consultant medical staff must be responsible for training and supervision of the staff carrying out cell salvage procedures.

### 3. SELECTION OF PATIENTS

Cell salvage is appropriate where there is a clean wound. The technique is applicable to open heart surgery, vascular surgery, total joint replacements, spinal surgery, liver transplantation, ruptured ectopic pregnancy and some neurosurgical procedures. Some Jehovah's Witnesses may accept transfusion of autologous cells salvaged by a continuous circuit device: specific consent to the procedure should be sought in this instance.

### 4. CONTRAINDICATIONS

Cell salvage techniques should not be used in the presence of bacterial contamination of the operative field. Malignant disease has been considered a contraindication but recent published work suggests that the risk of dissemination of malignant disease is minimal. Blood containing fat or amniotic fluid should not be salvaged because of the risk of embolism and DIC. Topical clotting agents such as collagen, cellulose, gelatine and thrombin, and topical antibiotics or cleansing agents used in the operative field should not be aspirated into a cell salvage device. Complications have been reported in patients with sickle cell disease.

5. Patients undergoing cell salvage need not be screened routinely for viral markers. Universal precautions to protect staff from the risks of virus transmission must always be observed. The used container and giving set must be disposed of in accordance with the hospital policy for the disposal of hazardous waste.

6. All blood salvage devices should be used in strict compliance with the manufacturers' instructions. The responsible consultant must ensure that a designated person is responsible for the maintenance of equipment, adherence to SOPs and documentation of all procedures.

7. Blood for reinfusion must be labelled according to the specifications given for ANH. Labelling, storage and disposal of salvaged blood must be in accordance with the standards outlines in paragraphs 2.8 above.

8. All cell salvage procedures and volumes of blood reinfused must be recorded in the patient's case notes. Where allogeneic blood is given, the reasons must be clearly documented in the patient's notes.

9. Serious adverse events should be reported to the hospital transfusion committee and to any appropriate national reporting system.

10. Regular audit of procedures should be undertaken under the aegis of the hospital transfusion committee. Audit and comparison with allogeneic blood usage would be facilitated by the routine recording of autologous blood use in theatre.

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## Disclaimer: BCSH Guidelines

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## Appendix 1

### "BLOOD COLLECTION"

The following points are important in collecting blood during preoperative haemodilution.

1. Blood may be collected into a single pack with CPD-A1 anticoagulant. (Licensed blood packs for collection of approximately 450 ml ±10% or 250 ml ±10% are available. Appropriate pack size selection is important to maintain anticoagulant to blood ratios. Some manufacturers may make dedicated packs.)

2. A regularly calibrated balance should be used to measure the volume of blood drawn.

3. Skin should be cleaned thoroughly using chlorhexidine (in alcohol) or equivalent.

4. The donor tubing should be clamped, for example with "non toothed" Spencer Wells forceps, before the guard is removed from the needle. The clamp should remain in place until after the venepuncture. This prevents air entering the bag and possibly contaminating the donation.

5. The blood pack should be labelled during donation.

The label affixed to the blood pack should include the following information:

Surname

First names

Date of birth

Hospital number

Date and time of collection

Responsible Medical Officer

UNTESTED BLOOD: FOR AUTOLOGOUS USE ONLY

6. The pack should be agitated gently throughout collection to mix the blood with the anticoagulant.

7. The bleed line should be sealed with clips or a heat sealer both at its cut end and close to the pack.

## Appendix 2

*Table 1* Indications, contraindications, potential adverse effects and methods of red cell salvage

| Technique | Indications | Contraindications | Potential adverse effects | Comments |
|---|---|---|---|---|
| Acute normovolaemic haemodilution | Elective surgery with expected loss >20% TBV | Aortic stenosis, unstable angina, left main stem disease or equivalent, moderate to severe left ventricular impairment | Requires adequate monitoring and maintenance of normovolaemia to prevent haemodynamic instability and possible myocardial ischaemia in susceptible patients | This is a widely available, low cost option with the potential advantage of a reduction in blood viscosity. Efficacy in reducing transfusion requirements has been questioned |
| Preop component collection (e.g. platelet-rich plasma) | | | | Research technique. Controlled studies have so far failed to confirm efficacy |
| Red cell salvage centrifugal processors | Elective and emergency surgery with expected loss >20% TBV | Bacterial contamination of wound; malignant disease; sickle cell disease and sickle cell trait are relative contraindications | In large volume losses risk of dilutional coagulopathy. Preventable with component Rx.<br>Training required for operator | Excellent long-standing safety record. Becomes increasingly cost effective with large volume losses. Some Jehovah's Witnesses will accept this. |
| Red cell salvage haemofiltration processors | As above | As above | Relatively new technology. Training required for operator. | Slower processing than centrifugal devices. Filter needs changing after 2 processing cycles |
| Red cell salvage single reinfusion devices | As above | As above | Safety and efficacy to be demonstrated by larger studies.<br>Worries concerning reinfusion of activated clotting factors, may increase risk of DIC | Simple and cheap for low volume losses |
| Red cell salvage mediastinal reinfusion | Postop. cardiac surgical patients emergency/elective | Sickle cell disease, bacterial contamination of wound | Worries concerning reinfusion of activated clotting factors, may increase risk of DIC | Unprocessed defibrinated blood transfused. Reduces banked blood requirements in patients with high mediastinal losses |

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# CORRESPONDENCE

## Use of rocuronium in a pregnant patient receiving magnesium medication

Sir,—The report by Gaiser and Seem[1] highlighted some important aspects of the use of non-depolarizing neuromuscular blocking agents in the presence of magnesium infusions. In their patient, the use of rocuronium for neuromuscular block was followed by prolonged paralysis. However, there are several problems with this report. The dose of rocuronium used was well in excess of the usual recommended dose of 0.6 mg $kg^{-1}$. The prolongation of non-depolarizing neuromuscular block by magnesium is so well known that the decision to use such a high dose of a non-depolarizing blocker needed to be very carefully considered. If it was known at the outset that the case was to last 6 h, then the use of rocuronium in these circumstances is acceptable, but prolongation of its action should have been expected. The validity of the choice of blocker is also open to debate. The evidence against the use of suxamethonium in patients with open eye injuries is, at best, weak. There is little hard evidence that the small increase in intraocular pressure (IOP) seen after the use of suxamethonium poses a real threat to the injured eye and several strategies are available to limit this increase in IOP.[2] In addition, magnesium decreases the fasciculations produced by suxamethonium,[3] and is likely to limit the increase in IOP consequent on suxamethonium use. The aspiration risk in this patient was clear, and it seems inappropriate to consider the minute risk of ocular injury from suxamethonium ahead of the hazards associated with the use of a non-depolarizing neuromuscular blocking agent.

The plasma concentrations of magnesium referred to in this case report must be wrong. I suspect that the units were erroneously quoted as mmol $litre^{-1}$ whereas the reported values are consistent with mEq $litre^{-1}$. It is extremely unlikely that, at the doses of magnesium given, the concentration in plasma would have been 5.8 mmol $litre^{-1}$. The correct therapeutic range is not 4–8 mmol $litre^{-1}$ as quoted in this article, but 2–4 mmol $litre^{-1}$. The quoted values tally with the normally quoted mEq $litre^{-1}$ range, those for molar concentrations being half the concentration reported when equivalents are used for divalent ions.

The important lesson of this report is that the well known interactions of magnesium and neuromuscular blocking agents should always be borne in mind. Careful selection of appropriate drugs and dosage is vital if this type of complication is to be avoided.

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Sir,—We appreciate the comments of James on our case report, especially those concerning the units for the plasma concentration of magnesium. In the original manuscript, it was mEq $litre^{-1}$. We apologize for the error in typesetting.

However, we disagree with several of his other statements. After initiating the case, we knew the neuromuscular blocking effects of rocuronium would be prolonged by magnesium; it was the extent with which we were unsure. In determining the risk and benefit of using rocuronium, we felt the benefit of avoiding the increase in intraocular pressure (IOP) outweighed the risk of possible postoperative intubation and ventilation should surgery conclude before its action had terminated.

He also states that the dose of rocuronium, 0.9 mg $kg^{-1}$ ($3 \times ED_{95}$), was excessive. As outlined in the manuscript, this dose, compared with 0.6 mg $kg^{-1}$, decreases the onset time to complete neuromuscular block by 50%.[1] In the pregnant patient who is prone to oxygen desaturation on induction, we felt that rapid securing of the airway to be most important.[2] As such, the higher dose was used.

Suxamethonium increases IOP by approximately 8 mm Hg. James stated that magnesium may attenuate this increase as magnesium would decrease the fasciculations produced by suxamethonium. Contraction of the extraocular muscles does not completely account for the increase in IOP. Pretreatment with a non-depolarizing neuromuscular blocking agent to prevent fasciculations does not reliably prevent this increase.[3] In fact, in patients scheduled for elective enucleation who had all of the extraocular muscles detached, suxamethonium still increased IOP.[4] Therefore, one would have to question if magnesium would limit the increase in IOP by suxamethonium.

Finally, James suggests the use of propofol and alfentanil to attenuate the increase in IOP. Although these agents may be helpful, it is important to remember that the patient was a 31-yr-old parturient with a 28-week gestation. Although propofol has been used successfully during pregnancy, it is not recommended.[5] There are no adequate and well-controlled studies concerning the use of alfentanil during pregnancy. Its use as a continuous extradural infusion during labour has been investigated. Neonatal hypotonia was observed.[6]

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## Hepatocellular integrity after inhalation anaesthesia

Sir,—In their study of hepatocellular integrity after inhalation anaesthesia, Tiainen and Rosenberg[1] found that GSTA concentrations increased in patients who received isoflurane or halothane, but the increase appeared greater in those receiving halothane. As they point out, this contrasts with previously published studies,[2 3] and they speculated on possible reasons for this. We believe the discrepancy between their findings and ours is explained by the use of different modes of ventilation in the two studies, and not from differences in the concentrations of agents administered.

There is little doubt that GST concentration measured by specific radioimmunoassay does not increase in normotensive, spontaneously breathing patients who receive isoflurane. Of the 18 patients who received isoflurane, only two showed an increase in GST concentration (4.1 and 4.3 μg $litre^{-1}$) after anaesthesia.[2] This confirmed results from a previous study in which no patient who received isoflurane showed an increase in GST concentration after anaesthesia.[4] In contrast, we have shown that the mode of ventilation significantly influences GST concentration more profoundly than the use of different volatile anaesthetic agents.[5] We studied 48 patients undergoing controlled hypotension for middle ear surgery who were allocated to one of four groups to receive either IPPV or SV, and halothane or isoflurane. GST concentrations increased at 1–3 h after the end of anaesthesia in all four groups but there was no significant difference in GST concentration between patients who had received halothane or isoflurane, irrespective of the mode of ventilation. Combining the results obtained using the two volatile agents allowed assessment of the effect of ventilatory mode and revealed that GST concentration was significantly greater at 1 h after the end of anaesthesia in patients who had received IPPV (pre-induction 2.3 μg litre$^{-1}$; 1 h 3.6 μg litre$^{-1}$) than in those who had breathed spontaneously (pre-induction 2.5 μg litre$^{-1}$, 1 h 2.6 μg litre$^{-1}$).

We do not consider that differences in concentration of volatile agents administered account for the differences observed between the study of Tiainen and Rosenberg and ours. We have never found that the change in GST from preoperative values is related to dose of anaesthetic agent or to duration of anaesthesia.

Murray, Rowlands and Trinick did not find any increase in GST concentration after isoflurane anaesthesia in patients who received IPPV.[3] We agree with Tiainen and Rosenberg that the likely reasons for this include the relatively insensitive GST assay used and infrequent sampling after anaesthesia. It should also be noted that whereas Murray and Tiainen's groups measured total alpha class GST (i.e. $B_1$ and $B_2$ subunits), we measured only GST $B_1$ subunits in our studies; measurement of $B_1$ subunits appears more sensitive than $B_2$ at detecting hepatic damage.

We believe that hepatocellular integrity is not impaired in spontaneously breathing patients who receive isoflurane, and that mode of ventilation has a greater influence on GST concentration after anaesthesia than the use of different inhalation anaesthetic agents.

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Sir,—Thank your for the opportunity to respond to the comments by Ray, Beckett and Allan concerning our study on hepatocellular integrity after isoflurane and halothane anaesthesia.[1] The two differences between our study[1] and that by Hussey and co-workers[2] were: (1) in our study there was no significant difference in GSTA between the isoflurane and halothane groups; and (2) in our study GSTA increased also in the isoflurane group. The latter fact may, indeed, have been caused by the influence of positive pressure ventilation in normotensive patients as seems to be the case in patients operated on under deliberate hypotension.[3] However, the former requires other explanations.

For about 9 yr it has been thought that halothane anaesthesia is usually associated with a disturbance in hepatocellular integrity while isoflurane anaesthesia is not.[2] Our study challenged this "truth".[1] We cannot totally reject our speculation that the former difference between the studies is caused by previous exposure to halothane or by differences in concentration of anaesthetics Halothane was probably more commonly used in Scotland in the 1980s than in Finland in the 1990s. The change in GSTA seems not to be related to the dose of anaesthetic agent or to duration of anaesthesia, but we have not found any study on GSTA comparing different concentrations of volatile anaesthetics, or comparing different durations of anaesthesia to prove these concepts Murray, Rowlands and Trinick[4] used a relatively insensitive assay and found a difference in GSTA concentration between halothane and isoflurane at 2 MAC for 10 h. There was also an increase in aspartate aminotransferase.[4] On the other hand, we found no significant difference between these anaesthetics at 1 MAC for 3 h.[1] In the studies in which Ray, Beckett and Allan have been co-authors,[2 3] the concentrations of volatile anaesthetics and the changes in GSTA concentration seemed to fall between these extremes.

We agree that positive pressure ventilation may be an important cause for the increase in GSTA after isoflurane anaesthesia but we need other explanations for the lack of difference between isoflurane and halothane. The increase in GSTA concentration after sevoflurane anaesthesia is also interesting because it occurs after positive pressure ventilation[5] but also after spontaneous ventilation.[6]

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## Safety issues and volatile agent analysers

Sir,—Drs Strachan and Richmond raised some interesting points in their case report concerning the presence of diethyl ether in an isoflurane vaporizer.[1]

Older Datex anaesthetic agent monitors are calibrated to measure levels of halothane, enflurane, isoflurane and methoxyflurane. It has been noticed in this hospital that when using sevoflurane the agent monitor seems to give readings corresponding to the vaporizer settings when set to measure methoxyflurane which is not seen when the agent monitor is set for any other volatile agent. This was purely a chance observation and has certainly not been used clinically as a monitoring method.

It does however seem surprising, given the different physical and chemical properties of sevoflurane (molecular weight 200.1, blood:gas partition coefficient 0.69, boiling point 58.6°C) and methoxyflurane (molecular weight 165, blood:gas partition coefficient 13, boiling point 105°C) and the seemingly closer similarity of sevoflurane to the routinely used volatile agents.[2] This must reflect similar infrared absorption bands of sevoflurane and methoxyflurane.

This would seem to indicate that in some circumstances two compounds with quite distinct properties can effect monitoring in similar ways given similar absorption spectra. This shows that advancing the scope of anaesthesia in one area must be paralleled by the ability to use appropriate monitoring techniques and, at best, monitoring is only an adjunct to clinical vigilance.

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## Ether in an isoflurane vaporizer and the use of vapour analysers in safe anaesthesia

Sir,—We read with interest the case report by Strachan and Richmond[1] and wish to make the following comments.

The ether-filled temperature compensation unit used in the PPV Sigma has been used safely in Penlon vaporizers for more than 40 yr and was one of the world's first automatic TC units, having been first introduced into the EMO vaporizer.

The design of the now obsolete PPV Sigma vaporizer discussed in the article necessitated a significant TC movement that was not possible to obtain by bimetallic expansion alone. That movement could only be provided by that type of liquid-filled expansion system.

The current range of Penlon Elite vaporizers makes use of significantly different control variables and as a result of these major design changes Penlon vaporizers no longer use liquid-filled TC units but do use a solid state bimetallic TC unit in common with some other manufacturers.

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1. Strachan AN, Richmond MN. Ether in an isoflurane vaporizer and the use of vapour analysers in safe anaesthesia. *British Journal of Anaesthesia* 1997; 78: 107–108.

## Non-invasive measurement of cerebral blood flow

Sir,—I read with interest the recent article by Gupta and co-workers.[1] It was only when I set out to derive the equations presented within this article that I realized that one of the definitions is wrong. The authors define CLVHR as "the coefficient of the large to small vessel packed cell ratio" whereas it is the inverse, the ratio of cerebral (small vessel) to large vessel haematocrits, as derived by Lammertsma and colleagues[2] and calculated as 0.69. It is the definition that is misleading, the equations are correct for the value quoted. Unfortunately, Gupta and co-workers have simply compounded the original error in definition given by Elwell and co-workers.[3]

My second comment is on the use of $F\mathrm{E}'_{CO_2}$ as equivalent to $Pa_{CO_2}$ when calculating carbon dioxide reactivity. First, the normal value for $Pa_{CO_2}$ is 5.3 kPa but this does not equate to an $F\mathrm{E}'_{CO_2}$ of 5.3 kPa. At rest, with quiet respiration, there is a small difference of 0.3–0.6 kPa between $Pa_{CO_2}$ and $F\mathrm{E}'_{CO_2}$. Thus data should have been indexed to a normal value for $F\mathrm{E}'_{CO_2}$, namely 4.85 kPa. The difference between $Pa_{CO2}$ and $F\mathrm{E}'_{CO_2}$ is important in the context of this study as respiration is altered to achieve different $F\mathrm{E}'_{CO_2}$ values. We are not told how the volunteers hyperventilated to reach a $Pa_{CO_2}$ of 3.5 kPa, but most people would increase ventilatory frequency and tidal volume may decrease; conversely, adding carbon dioxide to the gas mixture triggers hyperventilation largely by increasing depth of ventilation in addition to ventilatory frequency. As the difference between $Pa_{CO_2}$ and $F\mathrm{E}'_{CO_2}$ is dependent on tidal volume, the slope of the CBV *vs* $F\mathrm{E}'_{CO_2}$ line is no longer identical to the slope of the CBV *vs* $Pa_{CO_2}$ relationship. Physiologically, carbon dioxide reactivity is dependent on $Pa_{CO_2}$ not $F\mathrm{E}'_{CO_2}$ and so this source of error in determining carbon dioxide reactivity should be discussed as we are not told if the volunteers were asked to maintain a constant tidal volume for all parts of the study.

The lack of any significant change in packed cell volume in relation to $F\mathrm{E}'_{CO_2}$ is indeed puzzling when the calculated values for CBV are clearly related to $F\mathrm{E}'_{CO_2}$. Although the possibility of following changes in CBV non-invasively may be useful clinically, particularly for head injuries, to do this by altering $Pa_{CO_2}$ is not acceptable. It seems this point must be addressed before the methodology presented here is acceptable.

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1. Gupta AK, Menon DK, Czosnyka M, Smielewski P, Kirkpatrick PJ, Jones JG. Non-invasive measurement of cerebral blood volume in volunteers. *British Journal of Anaesthesia* 1997; 78: 39–43.
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3. Elwell CE, Cope M, Edwards AD, Wyatt JS, Delpy DT, Reynolds EOR. Quantification of adult cerebral hemodynamics by near-infrared spectroscopy. *Journal of Applied Physiology* 1994; 77: 2753–2760.

Sir,—I read with interest the article by Gupta and colleague[1], but have grave doubts on the validity of the conclusions regarding the ability to non-invasively assess cerebral blood volume, for several reasons.

First, no currently available near-infrared (NIR) spectroscopic system has the ability to completely exclude the scalp signal, which may potentially cause a great deal of artefact Second, the oxidized and reduced haemoglobin concentrations were derived from NIR absorption spectra by an algorithm, introducing a further potential inaccuracy. Third, calculation of $[Hb_{calc}]$ involves examining the changes in the derived signals, thereby compounding the error of an algorithm with the influence of the scalp tissue signal. Possibly this helps explain the 25% difference in the calculated cerebral blood volume (CBV) reactivities of 1.25 and 1.06 ml 100 $g^{-1}$ $kPa^{-1}$ when $HbO_2$ or $Hb_{diff}$ concentrations were used to perform the calculation. Fourth, CBV calculated in ml 100 $g^{-1}$ assumed a large number of variables to be constant. Haemoglobin was assumed to be 15 g $dl^{-1}$, even though five of 13 subjects were female and of an age likely to be menstruating. The coefficient of large to small vessel packed red cell ratio is assumed to be constant throughout, even though the authors noted that flow, as measured by transcranial Doppler, changed with moderate differences in oxygen content indicating vasoreactivity, which must surely change the large to small ratio.

Lastly, there is no "gold standard" with which the authors have compared their results, and although they may have measured changes in cerebral blood volume, one cannot be sure from this study.

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1. Gupta AK, Menon DK, Czosnyka M, Smielewski P, Kirkpatrick PJ, Jones JG. Non-invasive measurement of cerebral blood volume in volunteers. *British Journal of Anaesthesia* 1997; 78: 39–43.

Sir,—We thank Drs Hill and Williams for their comments.

In response to Dr Hill, we agree that the definition of CLVHR is the small to large vessel haematocrit ratio, as described by Lammertsma and colleagues.[1]

The study aimed to evaluate non-invasive methods of assessing cerebral blood volume. While we accept that there is a small difference in $Pa_{CO_2}$ and end-tidal carbon dioxide ($F\mathrm{E}'_{CO_2}$), arterial blood-gas monitoring was not used as described in the article. The data were indexed to the calculated CBV at an $F\mathrm{E}'_{CO_2}$ of 5.3 kPa. Although this does not equate to a $Pa_{CO_2}$ of 5.3 kPa, the regression equation of CBV reactivity should not be affected.

Further, the expression of CBV reactivity as a percentage of baseline CBV compensates for individual variations in baseline CBV. End-tidal carbon dioxide manipulation is a recognized method of measuring carbon dioxide reactivity[2] and is used clinically to assess carbon dioxide reactivity. However, we would not alter $Pa_{CO_2}$ to measure CBV in head injured patients. This is not implied in the study; we have used $Pa_{CO_2}$ variations in volunteers merely as a paradigm of CBV alterations in volunteers and these changes would result from spontaneous pathophysiological mechanisms in disease.

In response to Williams' comments, it is well recognized that there is extracranial contamination in the near infrared signal. It has been reported that there is approximately a 15% contribution of skin changes to the $HbO_2$ signal during carbon dioxide challenge, and much of this change is related to changes in systemic arterial pressure.[2] Our volunteers showed no significant change in MAP. It therefore seems unlikely that changes in skin blood flow contributed significantly to the carbon dioxide reactivity of the NIR signal. The use of an estimated Hb value and the approximations involved in the calculation may have biased the absolute level of CBV measured, but are unlikely to have affected reactivities.

While there is as yet no direct comparison of NIR measurement of CBV and CBV reactivity against the gold standard of positron emission tomography (PET), we have discussed our results in the context of data obtained by other authors and different techniques, including PET.[3]

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1. Lammertsma AA, Brooks DJ, Beaney RP, Turton DR, Kensett MJ, Heather JD, Marshall J, Jones T. In vivo measurement of regional cerebral haematocrit using positron emission tomography. *Journal of Cerebral Blood Flow and Metabolism* 1984; **4**: 317–322.
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## Tolerance of laparoscopy for resection of phaeochromocytoma

Sir,—In their report of two cases of intraperitoneal laparoscopic phaeochromocytoma resection, Mann and colleagues suggested that haemodynamic disturbance associated with pneumoperitoneum in one case may question the safety of this approach.[1] Such a conclusion cannot be justified on their evidence in which adequate preoperative preparation was given such a low priority.

They stated that 10 days preoperative treatment failed to provide satisfactory haemodynamic control in a patient, yet despite this, surgery was allowed to proceed. They then claimed that the hypertensive response to peritoneal insufflation in this patient reflected a risk associated with pneumoperitoneum rather than inadequate preoperative preparation. Notably, the second case (in which arterial pressure was stabilized before surgery with 20 days' treatment) showed no vasopressor response to pneumoperitoneum.

While no controlled, randomized study has been performed, it is generally agreed that preoperative preparation is the major factor in the reduction in perioperative morbidity and mortality and indeed preoperative therapy is mandatory in patients with sustained or paroxysmal hypertension.[2]

Their choice of antihypertensive drugs is also worthy of comment. They used nicardipine and, in the first case, labetolol. Calcium channel blockers such as nicardipine have been used in the perioperative period but cannot be regarded as "agents of choice" on the references quoted.[3 4] Labetolol is inadequate to control arterial pressure if large quantities of noradrenaline are released[5] and has been reported to cause paradoxical hypertension in patients with phaeochromocytoma[6] because of its potency at β relative to α receptors. Labetolol is therefore regarded as a poor choice of drug in the management of patients with phaeochromocytoma.

α-Adrenergic blockade, restoration of plasma circulating volume and β-blockade if required to control tachyarrhythmias are widely accepted for preoperative preparation.

Mann and colleagues refer to the retroperitoneal approach and apparent cardiostability of such cases, as reported by Giebler and colleagues.[7] It is worth noting that these patients were treated with phenoxybenzamine for 21 days before operation.

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1. Mann C, Millat B, Boccara G, Atgar J, Colson P. Tolerance of laparoscopy for resection of phaeochromocytoma *British Journal of Anaesthesia* 1996; 77: 795–797.
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Sir,—We thank Drs Jerwood and Willis for their interest in our investigation[1] but their letter deserves comment on two points: first, preoperative preparation, and second, effect of pneumoperitoneum.

We agree that no controlled, randomized study has demonstrated that preoperative preparation for phaeochromocytoma reduces perioperative morbidity and mortality. It is also not established that preoperative treatment should last at least 21 days to improve perioperative haemodynamic stability. Moreover, no preoperative preparation can control all perioperative haemodynamic events.[2] The issue of the need for any preoperative preparation has even been questioned elsewhere.[3] α-Adrenergic blockade requires time to be fully effective (this sometimes "justifies" up to 21 days of preparation!) and has many drawbacks: (a) arterial pressure instability when inducing treatment may delay the time of completing vasodilator therapy, (b) decreased venous tone and cardiac preload, and (c) increased risk of severe postoperative hypotension, especially with long-acting drugs such as phenoxybenzamine. In our experience, dihydropyridines allow short-term preoperative preparation,[4] do not induce arterial pressure instability, do not adversely affect venous return and cardiac preload, and do not cause severe postoperative hypotension. All of these features provide many reasons to choose dihydropyridines rather than α-adrenergic blocking drugs for preoperative preparation of phaeochromocytoma surgery.

Labetolol was used as a β-blocking drug, and it was added to a preliminary vasodilator therapy; therefore the risk of paradoxical hypertension was avoided.

In the first of the two case reports, peritoneal insufflation induced a severe increase in catecholamine concentration that mimicked adrenal tumour response to surgical manipulation. This is the evidence that insufflation of the pneumoperitoneum may induce direct stimulation of the adrenal tumour. Even 21 days of phenoxybenzamine preparation would not have avoided this catecholamine release from the adrenal tumour, as α-adrenergic blockade does not act on tumour secretion. Therefore, our conclusion is justified and we recommend caution with peritoneal insufflation for laparoscopic phaeochromocytoma resection.

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1. Mann C, Millat B, Boccara G, Atger J, Colson P. Tolerance of laparoscopy for resection of phaeochromocytoma. *British Journal of Anaesthesia* 1996; 77: 795–797.
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## Airway problems after carotid endarterectomy

Sir,—I read with interest the article by Munro, Makin and Read[1] describing four cases of acute respiratory obstruction after development of postoperative wound haematomas following carotid endarterectomy. They make the point that such patients require continuous respiratory monitoring in order to detect developing respiratory obstruction at an early stage. It is worth emphasizing that the neurological complications they refer to after carotid endarterectomy may include changes in respiratory function and control.[2] The presence of hypoventilation or even apnoea[3] would make the obstructive effect of postoperative haematoma even more rapid in onset. Gradual onset of respiratory obstruction may also lead to hypercapnia, which by means of the development of cerebral steal syndromes might lead to a decrease in blood flow in already ischaemic areas of the brain, thereby exacerbating the already compromised control of respiration. Inadequate control of arterial pressure in the postoperative period increases this effect in addition to increasing the size of postoperative wound haematomas.

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1. Munro FJ, Makin AP, Reid J. Airway problems after carotid endarterectomy. *British Journal of Anaesthesia* 1996; **76**: 156–159.
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## *In vivo* and *in vitro* dose–response curves

Sir,—Our Japanese colleagues[1] have made a good attempt in interpreting human anaesthetic dose–response curves at a molecular level. But they admit that not all the values they have derived are plausible. May I offer two suggestions?

They used the method of least squares, however, this has underlying assumptions that the data are Gaussian and homoscedastic, neither of which is true for quantal data. One method of analysing quantal data was described by Waud[2]: the appendix provides a simple BASIC program, which will solve equation (2) of the Osaka study. Waud's programme is translated easily into Microsoft Professional Basic, a language which overcomes most of the objections to old BASIC raised by computer professionals.

Second, the Osaka team suggested that the *in vivo* curve is the outcome of a normal, or log-normal, array of events at the molecular level. If so then their equation (2) would match reality better as a series, not a single unit:

$$y=\frac{x^{n_1}}{K_1{}^{n_1}+x^{n_1}}+\frac{x^{n_2}}{K_1{}^{n_2}+x^{n_2}}+\ldots$$

Adding one unit should reduce residual variance and the experiment repeated until there is no further improvement. With three units the solution would require inverting a 6×6 matrix, but that is no problem in Professional Basic, which has an efficient algorithm for any size of matrix.

Lastly, anaesthetics act on the synapse; if 1% halothane reduces transmission across each synapse to 70% of normal, then over a relay of five synapses it is decreased to 17% (0.7$^5$). Does it not follow that the *in vivo* curve should be steeper than effects at single synapses? This is why a simple reflex, such as withdrawing the foot, can be present when consciousness has been extinguished, as John Snow noticed 150 yr ago. May I wish them good luck with their endeavours.

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1. Iwai T, Kihara H, Imaiand K, Uchida N. Dose–response curve for anaesthetics based on the Monod–Wyman–Changeux model. *British Journal of Anaesthesia* 1996; 77: 517–521.
2. Waud DR. On biological assays involving quantal responses. *Journal of Pharmacology and Experimental Therapeutics* 1972; **183**: 577–607.

Sir,—We appreciate the letter of Dr Cormack which relates to our article on dose–response curves.[1] He suggests that assays of *in vivo* dose–response data have to be treated by the method of analysing quantal data, instead of the method of least squares, as described by Waud.[2] According to Waud's programme, we have re-examined the *in vivo* data and obtained revised results as follows: ED$_{50}$=1.01%atm (SEM=0.08%atm), $n$=3.59 (SEM=0.89) for isoflurane, and ED$_{50}$=0.76%atm (SEM=0.008%atm), $n$=29.2 (SEM=7.6) for halothane. These results are in agreement with those in our articles (ED$_{50}$=1.03%atm, $n$=3.6 for isoflurane; ED$_{50}$=0.75%atm, $n$=27 for halothane). Therefore, our least square fittings did not differ markedly from quantal assays.

Second, he suggests better fitting of data to the Hill equation (2) in our text by adding another unit. This may be effective for reducing residual variance, but the biological or molecular meaning of the adding term is not clear. Such a modification should be plausible when two or more doses are applied simultaneously,[2] or when some integrated effects take place on an organism, such as linkage effects between two or more receptor molecules each of which can bind with a drug molecule. In both cases, however, we have another problem, whether or not simple addition of one unit is suitable, because it depends on an adopted model.

Lastly, he mentioned an effect of a series of synapses. This is an interesting suggestion, but if there were a long series of synapses, only a small amount of dose applied would anaesthetize any patient. In other words, it cannot show the existence of a critical dose value above which a patient does not respond; the critical value is different between patients. In a complicated system of neurone networks, information propagates backwards in addition to forwards, and then some integrated response emerges. We suggest that this must be responsible for the existence of the critical dose value mentioned above. Although our MWC model oversimplifies the system, the model inherently has an integrated nature.

We thank Dr Cormack for his valuable suggestions and his interest in our article.

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## Ambulatory extradural analgesia in labour and mode of delivery

Sir,—Drs May and Elton[1] recently reported the results of a small prospective study comparing standard non-ambulatory extradural analgesia (boluses of 0.25% bupivacaine 10 ml) with ambulatory combined spinal–extradural analgesia (spinal bupivacaine 2.5 mg and fentanyl 25 μg followed by extradural top-ups of 0.1% bupivacaine 10 ml with fentanyl 2 μg ml$^{-1}$). They found that the rate of emergency Caesarean section was significantly lower in the ambulatory group (three of 30 *vs* 11 of 37; chi-square=3.89, $P$<0.05). If valid, this finding would be a major step forward for obstetric anaesthesia.

The first ambulatory, or mobile, extradural at the Royal Surrey

County Hospital was performed in late 1993. Because of the high rate (2.3%) of post-dural puncture headache after combined spinal–extradural analgesia reported by Collis and colleagues,[2] we adopted successfully a technique using extradural boluses of 0.1% bupivacaine 20 ml with fentanyl 2 $\mu$g ml$^{-1}$, without a spinal and without a conventional test dose. In 1996, 1100 (95.8%) of the 1148 extradurals (42.4% of labouring mothers) given for pain relief used this mobile technique, compared with one (0.11%) of 907 extradurals (35.2% of labouring mothers) in 1993.

Unfortunately, there has not been a reduction in the rate of emergency Caesarean section in mothers using extradural analgesia. In 1993, 78 (8.6%) of 907 mothers with extradurals required emergency Caesarean section compared with 146 (12.7%) of 1148 in 1996. This is a statistically significant increase (chi-square=8.8, $P<0.01$). However, there has also been a significant increase in the number of mothers having a spontaneous vaginal delivery, from 432 (47.6%) in 1993 to 646 (56.3%) in 1996 (chi-square=15.9, $P<0.001$) and a significant decrease in the number of instrumental deliveries, from 397 (43.8%) in 1993 to 356 (31.0%) in 1996 (chi-square=35.5, $P<0.001$). In those mothers who did not receive an extradural, the rates of spontaneous vaginal delivery, instrumental delivery and emergency Caesarean section have not changed significantly between 1993 (85.4%, 5.3% and 9.3%, respectively) and 1996 (87.8%, 4.2% and 8.0%, respectively). A randomized study by Collis, Davies and Aveling[3] comparing ambulatory combined spinal–extradural analgesia with standard non-ambulatory extradural analgesia found no difference in the outcome of labour. However, Asselineau[4] observed a significantly lower instrumental delivery rate but similar Caesarean section rates in the ambulant group when comparing ambulant and non-ambulant extradurals. Experience at this hospital suggests that the use of mobile, or ambulatory, extradurals may lead to a higher rate of spontaneous vaginal delivery and a lower rate of instrumental delivery.

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Sir,—We thank Dr Jenkins for his interest in our small randomized study[1] comparing extradural analgesia using 0.25% bupivacaine with a previously described combined spinal–extradural (CSE).[2] His large retrospective audit of extradural technique and mode of delivery confirmed the findings of some,[3 4] although not all, studies.[5 6] We appreciate his anxiety about the use of the subarachnoid component of this technique with regard to reports of meningitis after CSE in labour.[7] The evidence for an increased incidence of post-dural puncture headache is however not so clear.[8] It is possible that the ability to provide pain-free ambulation in labour may be beneficial if it is produced using an extradural only technique or a CSE. We have recently commenced a much larger collaborative study with colleagues at Birmingham Women's Hospital comparing these techniques and we hope this will demonstrate if the spinal component of a combined spinal–extradural is essential for the beneficial effect suggested in our study.

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2. Collis RE, Baxandall ML, Srikantharajah ID, Edge G, Kadim MY, Morgan BM. Combined spinal epidural (CSE) analgesia: technique, management and outcome of 300 mothers. *International Journal of Obstetric Anaesthesia* 1994; 3: 75–81.
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## The "Dumfries claim"

Sir,—The reference to the first trial of ether anaesthesia at Dumfries and Galloway Royal Infirmary on 19 December 1846 (in your editorial[1]) is dismissive and, as such, deserving of comment. In an allusion to William Scott's assertion of priority over Robert Liston with regard to the date, Professor Spence refers to the "Dumfries claim", quoting, I presume, the title of my original paper in your journal.[2]

The "claim", as Professor Spence correctly stated, was contained in William Scott's letter to *The Lancet*[3] on October 19, 1872, one of the no fewer than three reliable references to the validity of Scott's assertion. While the question of precedence was an important personal issue for William Scott, at no time did he infer that his early application of anaesthesia at Dumfries had any influence on the rapid acceptance of ether. Nevertheless, had James Y. Simpson been in Edinburgh at the time, in which case the news of Scott's operation would have reached him almost immediately, the Old World would doubtless have been informed of the anaesthetic properties of ether through alternative channels! In that case, Robert Liston might well have had to share the honours with his colleagues in south-west Scotland.

The suggestion by Professor Spence that James Y. Simpson travelled to London "for the specific purpose of learning about anaesthesia" would appear to be incorrect. Simpson's journey to London in December 1846 was the first of two visits in connection with his appointment as surgeon to Her Majesty Queen Victoria's household in Scotland and, on the date of the Squire:Liston success, he was either on his way to, or had already arrived in, London. He received the news of ether, therefore, not from London but in London.

The narrative surrounding the Dumfries operation is a fascinating one and has been the subject of several publications by this writer over the past 30 yr.[4 5] The gentlemen at Dumfries provided the chronicles of anaesthesia with a remarkable story and the fact that particulars regarding the patient are, as yet, incomplete does not lend the right to dismiss the incident with, "the outcome, whatever it was, adds nothing to science or medicine".

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3. Scott W. The exhibition of ether as an anaesthetic. *Lancet* 1872; 585.
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5. Baillie TW. *The Dumfries Ether Diary.* Dumfries: Creedon, 1996 (ISBN 1 899 3316 353).

Sir,—Writing from this address about the arrival of ether anaesthesia in Britain, what is one to do? Having mentioned Dumfries, thus hoping to avoid the letters that would have been sent had I failed to do so, it was necessary to give a brief evaluation of the significance of the event.

I am grateful to Dr Baillie for drawing attention to the revised account of Simpson's movements around Christmas, 1846. Dr Baillie will understand that I did not have the benefit of his interesting 1996 book[1] until after the editorial had been published. As it happens I had been guided by the sentence "no sooner had word of the first successful demonstration of surgical anaesthesia in London reached the Scottish capital than Simpson was on his way south." This is taken from Dr Baillie's 1966 book.[2] Even if Simpson had remained in Edinburgh in the relevant days, it is difficult to know how he might have been the vehicle through whom the Old World would have heard the news The problem of the "Dumfries claim" is one of non-communication. Simpson was just as much in the dark as everyone else

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1. Baillie TW. *The Dumfries Ether Diary*. Dumfries. Creedon, 1996 (ISBN 1 899 3316 353).
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## Allergies and anaesthesia

In their case report,[1] Rae, Milne and Wildsmith highlighted the importance of obtaining a detailed history, particularly in the area of allergies. I recall a similar case also during a Caesarean section under regional anaesthesia which reinforces this point.

A 35-yr-old ex-nurse, with atopy but no known allergies, underwent a routine combined extradural–spinal anaesthetic for elective Caesarean section. Catheterization with a latex urinary catheter was uneventful. Just after delivery and a bolus of i.v. oxytocin she complained of "feeling unwell' and said her tongue "felt swollen", she developed an erythematous rash on her upper body with visible facial oedema and her arterial pressure rapidly became unrecordable. A diagnosis of anaphylaxis was made; amniotic fluid embolus was part of the differential diagnosis. Treatment with oxygen, i.v. crystalloid and adrenaline rapidly restored her to her previous state. A similar, but less severe, episode occurred before surgery was completed. Recovery was uneventful, the urinary catheter was removed 24 h after operation.

It was only afterwards on direct questioning that the patient described past episodes of facial swelling on blowing up balloons, contact dermatitis to rubber gloves and vaginal irritation to condoms. Skin prick testing proved highly positive for latex, and negative for oxytocin, bupivacaine and Gelofusine.

This case also demonstrates that the risk of latex allergy in medical staff (2.8%) is greater than that found in patients presenting for skin prick tests (0.8%) although theatre staff are at greatest risk (7.8%).[2] Repeated latex exposure is believed to be responsible for these observations.

Latex-containing products release variable amounts of antigen (water-soluble proteins), examination gloves and urinary catheters releasing far more than surgical gloves. This may explain why anaphylactic reactions associated with the former commonly occur within 2–3 min, as in Rae, Milne and Wildsmith's case, while those associated with surgical gloves contacting the large absorptive surface of the abdomen (the commonest reported route) often take longer to develop, typically 40–300 min,[3] as in the above case. Why the two patients reacted so differently I am at a loss to explain.

Since the original case report[4] latex sensitivity has become recognized as a relatively common cause of allergic dermatitis and anaphylaxis. This may be caused by a combination of change in the manufacturing process, greater antigen exposure, heightened clinical awareness and more frequent use of latex as an antigen during investigations of drug reactions. Whatever the cause it is necessary to inquire about latex sensitivity from all of our patients to avoid similar scenarios.

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3. Gold M, Swatz JS, Braude BM, Dolovich J, Shandling B, Gilmour RF. Intraoperative anaphylaxis: An association with latex sensitivity. *Journal of Allergy and Clinical Immunology* 1991; 87: 626–666.
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*British Journal of Anaesthesia* 1997; 78: 779–780

# BOOK REVIEWS

*Airway Management.* L. H. HANOWELL AND R. J. WALDRON (eds). Published by Lippincott-Raven, Philadelphia. Pp. 480; indexed; illustrated Price £73.00.

This is a new text with contributions from authors based mainly in California, Texas, Alberta and various parts of Australia. Many of the chapters are multi-authored and the general effect of this appears to be to increase the effectiveness rather than cramp the style There is a clear attempt to provide an authoritative review rather than a simple listing of the large number of relevant references. A UK reader will be interested in the meat of the text and find the relatively standard pharmaceutical contributions (i.e a chapter each on i.v. anaesthetics, inhalation anaesthetic agents, neuromuscular block and opioids) out of place, especially as there is little direct application specific to the main thrust of the text.

The description of algorithms and "what to do next" was handled sympathetically and advice generally constructive, presumably reflecting the multi-authorship. The practical descriptions of the less common techniques were detailed clearly with appropriate illustrations. There was extensive cover of most of the specialist clinical areas associated with difficult airway My personal view is that in many of these areas the anaesthetist tends to take more of a leading role than in most other clinical situations and needs not only to be diagnostically aware but also able to determine imaging requirements appropriate to the anaesthetic rather than just surgical needs. This needs to be reflected more clearly when describing acute airway events in major ENT and faciomaxillary surgery.

It is particularly surprising, especially in view of the title of the book, that so little space is devoted to the many problems posed by sleep apnoea and its medical and surgical management. This is especially surprising when there is a whole chapter on routine medical considerations for lower airway obstruction caused by asthma Although relatively short, there is a thought provoking chapter on blunt trauma and the major airways and the important diagnostic and management difficulties that may be encountered in these patients. Overall the chapter on cervical spine injury is fairly balanced but there is a section devoted to advice on ATLS nasal intubation in some detail, that ends with a cautionary tale. This is followed immediately by advice about fibreoptic intubation. Although it is stated that a difference between elective and emergency cases is important there is also an implication that the answer is "skilled hands and proper patient selection".

Overall I found parts of this textbook informative and interesting. I doubt that many anaesthetists in the UK would want to purchase it for their own personal use because of what will be seen as redundant material which is dealt with better in other standard anaesthetic texts. It would be easy to recommend it for purchase by postgraduate medical libraries because of the extensive coverage of less common techniques. At the same time, however, there are several other texts available at present and whether or not this holds a place against the competition in the longer term remains to be seen.

*P Charters*

*Essentials of Anesthesiology*, 3rd Edn D. C. CHUNG AND A M. LAM. Published by WB Saunders, Philadelphia. Pp. 351; indexed; illustrated. Price £22 95.

This text is intended to be a pocket book for the trainee doctor in anaesthesia and aims to provide basic knowledge of general anaesthesia. The authors accept that the text is not comprehensive and subspecialties are not covered. The range of topics covered is comprehensive and up to date with particularly good chapters on blood transfusion, quality assurance and risk management, and airway management.

This book is designed to complement the lectures, tutorials and theatre teaching which the beginners receive in the first 3 months. It therefore fulfils this objective by the use of short, clear sections with an adequate number of diagrams, tables and illustrations.

This book is very enjoyable to read. It is not a book which will benefit examination candidates. Its English is simple, the diagrams are very illustrative and clear and I would recommend it to those who are beginners in anaesthesia.

Although based on American practice, this does not detract from the value of the book for a trainee working in anaesthesia anywhere in the world. It certainly represents good value for money.

*I Jeyapalan*

*The Adult Spine, Principles and Practice*, 2nd Edn. J. W. FRYMOYER (ed). Published by Lippincott-Raven, Philadelphia. Pp 2443; indexed; illustrated. Price £257.00.

These two volumes constitute as complete a text as a spinal surgeon could wish to have. The specialty of spinal disorders has grown enormously in recent years. Afflictions of the axial skeleton overlap and impact on most specialties within medicine and this text should be available in all quality medical libraries.

Pain management specialists would be particularly interested in the chronic pain chapters. The overall approach is evidence-based but individual authors give their own perspective on treatment modalities. The history, epidemiology and economics sections give the reader an insight into how we have arrived at the present epidemic of back pain. Chapters on functional restoration and pain management programmes are by world authorities and the handy hints contained within could well enhance the limited and oversubscribed services of this nature in the UK. There is a wealth of quality information relating to spinal disability. I would strongly recommend these volumes to anaesthetists with an interest in pain management.

There is plenty for the spinal surgeon; there is little for the spinal anaesthetist except for one chapter on anaesthesia and postoperative pain management. Issues are aired in the most general of terms. Cord monitoring is covered briefly and the Stagnara wake-up test is described. The concept of the surgeon giving advance notice of 30–45 min assumes a degree of temporal awareness that is unlikely in most orthopaedic surgeons. Surgery of the paediatric spine is not within the scope of the book and so the anaesthetic challenges relating to this are quite reasonably not covered

The invited authors of chapters are international experts, mainly American. Some differences in indications for surgery are apparent and fascinating. An example would be surgery for sciatica occurring at 3–4 weeks in America rather than the more traditional 6 weeks to 6 months in the UK.

This is a high quality, comprehensive, multi-author text that all medical libraries should possess as a standard reference for disorders of the axial skeleton. Individuals with a specific interest in the adult spine may well wish to have their own copy.

*P. Sell*

*Clinical Notes for the FRCA.* C D DEAKIN Published by Churchill Livingstone, Edinburgh. Pp. 308; indexed; illustrated. Price £17.50

This book has been written as a revision aid for candidates preparing for the final FRCA examination. On the whole it is written in a lecture notes format supplemented with bulleted lists, tables and good illustrations.

The book is divided into 12 chapters. The first three cover the problems of anaesthetizing patients with cardiac, respiratory or neurological disease. The next two chapters are titled "other systems" and "metabolism". These cover a range of subjects, including anaesthesia for all the major surgical specialties and the anaesthetic considerations of particular diseases, including diabetes, obesity and phaeochromocytoma. The next chapter on "miscellaneous" topics is a pot pourri of subjects from anaesthesia for Jehovah's Witnesses to resuscitation, including a brief section on statistics. Additional chapters cover intensive care, obstetrics and paediatric anaesthesia, pain, general pharmacology and equipment Each chapter is supplemented by references which direct the reader to the most recent reviews or textbook chapters which cover the subjects in more detail. The final chapter contains summaries of the most recent national reports of interest to anaesthetists, including NCEPOD and the Confidential Enquiries into Maternal Deaths.

Personally, I liked this book; it is well written, concise and full of useful information. This is not a book for the beginner or for someone who has not read any other textbooks covering anaesthetic specialties. However, it is an extremely useful revision aid, not to be read from cover to cover, but to be dipped into as a quick and portable reference. Although it is more than 300 pages long it fits easily into a briefcase or handbag and is very competitively priced. I am sure it will become a favourite of many trainees.

*A. Ogilvy*

*Anatomy for Anaesthetists*, 7th Edn. H. ELLIS AND S. FELDMAN. Published by Blackwell Science, Oxford. Pp. 374; indexed; illustrated. Price £59.50.

Any book that reaches its seventh edition in less than 25 yr is clearly successful and this is one of the classic books related to anaesthesia to have been produced in modern times. It presents regional anatomy in a manner and sequence that is entirely appropriate to our specialty, and the text, although relatively brief and lacking some detail, is informative and relevant. The illustrations continue to be superb and an object lesson in what can be achieved with clear line diagrams supplemented by carefully thought out shading and minimal use of colour. A superficial examination of the volume suggests that the original drawings from the early editions continue to be used, but I note that they have been re-drawn and this has given them a freshness that prevents the book from looking dated. The volume is nicely produced and I am sure that many anaesthetists will continue to feel that it is an essential component of a personal library.

However, I have some concerns. *Anatomy for Anaesthetists* has always worked well as a source of information on the anatomy that is relevant to our specialty, but it does less well when it strays towards the clinical implications of that anatomy. The unfortunate illustration in the sixth edition that showed a laryngeal mask airway with the concave curvature of the cuff facing posteriorly has been modified but it still does not portray the airway accurately. This may not be of great clinical significance, but there are some much more unfortunate illustrations relating to peripheral nerve blocks. This is particularly true of the section relating to brachial plexus block. If the example of the illustrations was to be followed a pneumothorax would almost be guaranteed and this is most unfortunate given that many trainees are advised to learn their anatomy from this book. My feeling is that the authors should restrict themselves to describing the relevant anatomy (with which they are clearly very familiar) and leave descriptions of clinical block techniques to others. There is significantly more to regional anaesthesia than anatomy, although it would be helpful if there were more descriptions of the fascial planes and sheaths that are encountered during block needle insertion at many sites.

At nearly £60 it is relatively expensive compared with more modern texts of anatomy which base their illustrations on modern imaging technique such as computed tomography and magnetic resonance imaging. However, I feel that the simple line diagram when executed correctly conveys the essence of anatomy which otherwise can be lost in a mass of detail. I just wish that the authors would confine themselves to anatomy.

*J. A. W. Wildsmith*

*Essays on the History of Anaesthesia. International Congress and Symposium Series 213.* A. M. BARR, T. B. BOULTON AND D. J. WILKINSON (eds). Published by The Royal Society of Medicine Press, London. Pp. 226; indexed; illustrated. Price £15.50.

The History of Anaesthesia Society first met in 1986, and now has a membership in the region of 500. Members of the society enjoy a limited circulation booklet containing the proceedings of each meeting. These are useful to keep, but they are not indexed, and the quality of production, although quite satisfactory for the original purpose, is of a modest standard. This new collection of essays represents papers presented to the society in the period 1986–1989. The editors have made a selection, so that the book does not replace the proceedings. Some of the papers have been revised and updated with new illustrations, but it is not clear to what extent or why this was done. Some papers cover a wide scope, while others relate to what are very minor topics. All are nicely presented and are an enjoyable read. I am glad the editors have undertaken this task. Not only is the work a useful contribution to the history of medicine, but for many of us there are papers by and recollections of friends and colleagues who have died since the History of Anaesthesia Society was formed. One hopes this volume is indeed the first of a series.

*A. A. Spence*

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